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Archives of Internal Medicine

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THE MECHANISM OF PERIPHERAL STASIS IN MYOCARDIAL INSUFFICIENCY

CAPILLARY AND VENOUS PRESSURES *

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AND
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The peripheral manifestations, such as hepatic and pulmonary congestion, engorgement of the veins and edema, that accompany an impaired circulation are conventionally explained by assuming that with the failing heart action there is a rise in pressure in the right auricle which impedes the venous flow to the heart; that this, in turn, causes engorgement of the veins and a heightened venous pressure which eventually is transmitted to the capillaries. "The increased venous pressure spreads to the peripheral parts, acting not only so as to dilate the peripheral vessels, but also to retard the capillary flow. The increased capillary pressure results in an exemia or filtration of fluid into the capillary spaces, which is responsible for the edema and ascites on the one hand, and the concentration of blood evidenced by polycythemia on the other." [1]

Measurements of the venous pressure in patients with myocardial insufficiency have been adduced to support this view. Clark,[2] using Hooker's method, and Moritz and von Tabora,[3] Schott [4] and Marks,[5] using the direct method devised by the first of these authors, all report an elevation of venous pressure in cardiac insufficiency. Clark found that a rise in pressure may precede the clinical signs of cardiac failure,

* From the Medical Division, Montefiore Hospital for Chronic Diseases.

1. Wiggers, C. J.: Nelson's Loose-Leaf Living Medicine **4**:259, 1920.

2. Clark, A. H.: A Study of the Diagnostic and Prognostic Significance of Venous Pressure Observations in Cardiac Disease, Arch. Int. Med. **16**:587 (Oct.) 1915.

3. Moritz, F., and von Tabora, D.: Ueber eine Methode beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, Deutsch. Arch. f. klin. Med. **98**:475, 1910.

4. Schott, E.: Die Erhöhung des Druckes in venösen System bei Anstrengung als Maas für die Funktionstüchtigkeit des menschlichen Herzens, Deutsch. Arch. f. klin. Med. **108**:537, 1912.

5. Marks, H. E.: The Clinical Determination of Venous and Capillary Pressures, Med. Clin. N. A. **4**:239, 1920.

and Schott that the rise in venous pressure after exercise is proportional to the degree of insufficiency of the heart.

A similar elevation of the capillary blood pressure has been noted by several authors, notably by Krauss [6] and von Basch.[7] The method for the determination of the capillary pressure that was employed by both of these authors, however, depended on the paling of the skin when measured pressure was exerted upon it. It has been shown that this technic is quite inaccurate, and their conclusions, therefore, have little value.[8] Recently, however, Liebesny,[9] employing a more accurate method, has reported an elevation of capillary pressure in patients with venous stasis.

Sir James Mackenzie [10] has called into question the back pressure theory of heart failure and has pointed out that the primary cause of a failing circulation is weakness of the heart muscle. He says:

> The objective signs of heart failure, such as dropsy and venous and hepatic engorgement, are usually spoken of as signs of back pressure; but they are probably due to an inefficiency of the driving power. The blood passes through the capillaries at a slow rate, impairs their nutrition, and allows transudation to take place, which we call dropsy. Under certain circumstances, this enfeebled circulation leads to great engorgement of the venous side of the circulation. Dilatation of the tricuspid and venous orifices may arise, so that we get regurgitant waves of blood sent back into the veins and the liver by contraction of the auricle and ventricle. Under these circumstances "back pressure" does modify the circulation and produce definite symptoms. But these results occur in only a small proportion of cases of heart failure, and by the time they appear the heart failure has reached an advanced stage.

The chance observation that in several patients with myocardial insufficiency the readings of capillary blood pressure were low drew our attention to this problem. We have therefore studied a series of nineteen patients, noting the clinical signs and symptoms and measuring the venous and capillary pressures. Most of the patients were reexamined at an interval of several weeks. For the venous pressure determinations we followed the technic of Moritz and von Tabora,[8] the most accurate one that has been described. Measured by this method the normal figures for venous pressure range from 1 to 10 cm. of water, most frequently from 4 to 8 cm., with an average figure of 5.2 cm. With cardiac insufficiency the figures may rise to 20 or 25 cm. of water. Their highest reading was 32 cm. For the capillary pressure determina-

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6. Krauss, H.: Der Kapillardruck, Samml. klin. Vorträge (inn. Med.) **13**: 315, 1914.

7. Von Basch, S.: Experimentelle und klinische Untersuchungen über den Capillardruck, Internat. Beitr. z. inn. Med. **1**:65, 1903.

8. Danzer, C. S., and Hooker, D. R.: Determination of the Capillary Blood Pressure in Man with the Microcapillary Tonometer, Am. J. Physiol. **52**:136 (May) 1920.

9. Liebesny, P.: Die Capillardruckmessung beim Menschen, Klin. Wchnschr. **2**:521, 1923; Arch. f. d. ges. Physiol. **198**:215, 1923.

10. Mackenzie, J.: Diseases of the Heart, Ed. 3, London, 1913, p. 26.

tions we employed the method described by Danzer and Hooker,[8] which we have been using in our other studies of capillary pressure. For details reference may be had to the original communication of Danzer and Hooker and to our first paper.[11] The normal capillary pressure, as determined by this method, is about 20 mm. of mercury, but the readings in different capillaries in the same person and in different normal persons may vary from 5 to 30 mm. of mercury. Cases in which most of the readings are above 25 or below 10 are rare.

In all cases the venous pressure was first estimated, and the capillary pressure was measured from thirty to sixty minutes later. The capillary pressure was measured with the patient in a sitting posture with the hand at heart level. Our observations are presented in Table 1.

In Cases 1 to 5 the patients showed a heightened venous pressure accompanied by a normal capillary pressure which had a tendency to be low. They all gave clinical evidence of definite myocardial insufficiency. The patients in Cases 6 to 12 presented normal venous and capillary pressures. In them the signs of failing circulation were less evident. Cases 13 to 16, in which high venous pressures are associated with high capillary pressures, are more difficult of interpretation. They are, with one exception, cases of hypertension which have consistently shown high capillary pressures. The capillary pressure in Case 13, of which we have records for the past two years, has always been high. The patient in Case 15 was observed over a period of one year, and he had consistently high capillary pressure readings even at a time when he gave no evidence of circulatory failure. The patient in Case 16 is the only one of a series of 130 whom we have observed exhibiting a normal blood pressure and a high capillary pressure; yet her venous pressure barely exceeds the normal. In view of our other observations we do not believe that in this group of cases the elevation of capillary pressure is determined by the increased venous pressure. The patient in Case 17, with hypertension, a low venous pressure, and a high capillary pressure confirms this opinion.

It is worthy of note that in those patients in whom studies made on two occasions showed a significant variation of venous pressure, there was no constant parallel alteration of the capillary pressure.

In an attempt to obtain further information of the effect on the capillary pressure of a heightened venous pressure the following experiment was performed: A young man with healthy circulatory organs was placed on his back on an examining table in such a position that simultaneous readings of venous and capillary pressures could be made. A blood pressure cuff attached to a mercury manometer was placed around the arm that was used in the examination, and the hand was

11. Boas, E. P., and Frant, S.: The Capillary Blood Pressure in Arterial Hypertension, Arch. Int. Med. **30**:40 (July) 1922.

TABLE 1.—*Observations on Authors' Patients*

Case	Date	Diagnosis	Venous Pressure, Cm. of Saline	Range of Capillary Pressure, Mm. of Mercury	Number of Capillary Readings	Blood Pressure	Myocardial Insufficiency	Comment
1	3/22/23	Rheumatic heart disease; mitral stenosis; aortic insufficiency; auricular fibrillation	29.3	17 - 31	19	178/ ?	Severe	Dyspnea; orthopnea; cyanosis; distended veins; edema
	5/29/23	.....	33.1	4 - 13 15 - 20	20 4	220/130	Severe	Marked dyspnea; orthopnea; cyanosis; distended veins; ascites; edema of feet and back
2	3/27/23	Myocardial degeneration; chronic nephritis; chronic bronchitis	15.5	5 - 6 10	18 3	144/ 84	Severe	Dyspnea; general cyanosis; ascites; edema
3	3/27/23	Rheumatic heart disease; mitral stenosis; auricular fibrillation	14.4	13 3 - 4	2 11	138/ 82	Moderate	Cyanosis; distended veins; slight dyspnea
	5/23/23	.....	16.4	5 12 - 17	10 13	140/ 80	Moderate	Condition slightly improved
4	4/10/23	Chronic bronchitis; hypertension; cardiac dilatation and hypertrophy	12.1	5 10 - 12	2 5	180/120	Severe	Orthopnea; marked cyanosis; distended veins; ascites; edema
5	4/23/23	Rheumatic heart disease; mitral stenosis; aortic insufficiency; auricular fibrillation	11.2	5 - 8 12	9 1	.....	Moderate	Cyanosis; slight dyspnea; distended veins
	5/10/23	.....	11.4	6 - 10	8	132/ 88	Moderate	No change
6	5/23/23	Bronchiectasis; cardiac hypertrophy and dilatation	10.1	3 10	6 11	140/ 90	Slight	Slight cyanosis and dyspnea
	5/10/23	.....	7.3	3	12	.....	Slight	No change
7	4/23/23	Exophthalmic goiter; auricular fibrillation	8.2	10 - 13 23 - 30	8 4	150/ 76	Slight	Asthenia; slight dyspnea
	5/23/23	.....	10.4	14 - 15	9	148/ 70	Slight	No change
8	4/ 9/23	General arteriosclerosis; hypertension.....	7.9	5 17	8 1	184/ 90	Slight	Slight cyanosis; slight distention of veins
	5/ 9/23	.....	5.2	5	10	170/ 90	Slight	General condition improved

9	4/15/23	Syphilitic aortitis; aortic insufficiency; cardiac hypertrophy	5.7	10	4	120/ 42	Slight	Slight cyanosis
	5/ 7/23	.....	7.8	3 - 4	11	118/ 32	Slight	Condition unchanged
10	4/13/23	Rheumatic heart disease; mitral stenosis; aortic insufficiency	5.8	5 - 8 10	10 1	150/ 50	Severe	Marked cyanosis and dyspnea; distended veins; edema
	5/ 7/23	.....	3.9	9 - 10 16 - 23	14 9	130/ 44	Severe	No change in condition
11	3/30/23	Bronchiectasis; chronic bronchitis; cardiac hypertrophy and dilatation	4.9	7 - 15 3 - 5	16 8	140/ 85	Moderate	Dusky cyanosis; dyspnea; distended veins
	5/ 9/23	.....	2.6	5 - 12	10	126/ 76	Moderate	Slight edema
12	4/13/23	Chronic bronchitis; emphysema; cardiac hypertrophy and dilatation	3.1	26 - 28 17 5	8 2 3	172/ 98	Moderate	Cyanosis; dyspnea
	5/ 7/23	.....	3.6	10 - 16 5	4 10	158/ 98	Moderate	No change
13	3/29/23	Hypertension; myocardial degeneration; auricular fibrillation; bronchiectasis	19.4	40 - 47	37	220/110	Severe	Dyspnea; cyanosis; distended veins; edema
	5/23/23	.....	17.4	42 - 48	20	.....	Severe	Slight increase in edema
14	3/30/23	Myocardial degeneration; general arteriosclerosis; chronic nephritis	14.4	20 - 45 100 +	28 5	140/ 95	Severe	Dyspnea; cyanosis; distended veins; edema; pulsus alternans
	7/ 9/23	.....	9.7	8 - 9 13 - 28	3 13	.....	Severe	Gallop rhythm; edema
15	3/29/23	General arteriosclerosis; chronic nephritis; hypertension; cardiac hypertrophy and dilatation	10.7	40 - 80 21	9 1	200/140	Severe	Puffiness of face; dyspnea; edema
16	5/ 2/23	Chronic nephritis	9.9	40 - 60	12	120/ 80	Slight	Nephritic facies; slight edema
	5/23/23	.....	11.7	25 - 33	7	.....	Slight	No change
17	4/ 5/23	Hypertension; cardiac hypertrophy and dilatation	6.0	45 - 55 32 - 36	6 6	220/120	Slight	Slight cyanosis and dyspnea
	5/10/23	.....	4.5	28 - 44	26	212/136	Slight	No change
18	4/13/23	Chronic bronchitis and emphysema; cardiac hypertrophy and dilatation	9.8	8 13 - 15	1 6	120/ 78	Moderate	Marked cyanosis; dyspnea; distended veins
	5/ 9/23	.....	8.8	11 - 13	5	140/ 78	.....	No change
19	3/22/23	Rheumatic heart disease; mitral stenosis; aortic insufficiency; auricular fibrillation	9.1	21 - 31	16	148/ 80	Severe	Dyspnea and cyanosis; distended veins; pleural effusion; edema
	5/ 9/23	.....	14.9	15 - 28	15	150/ ?	Severe	General condition about the same

placed at heart level. The venous pressure manometer was filled with 2 per cent. sodium citrate solution to prevent clotting of blood in the needle which was left in the vein over a considerable period of time. Control readings were made until both venous and capillary pressures were stabilized. Then the blood pressure cuff was inflated with air up to a certain point and maintained at that pressure while repeated readings of the venous and capillary pressures were made. The same group of capillaries were always used for the pressure estimations. The experiment was performed on three different days with similar results. Table 2 gives a protocol of the last session.

TABLE 2.—*Pressure Estimations*

Time	Pressure in Sphygmomanometer Cuff, Mm. of Mercury	Venous Pressure, Cm. of Citrate	Capillary Pressure, Mm. of Mercury
2:30 to 2:40	0	8.1	17
	"	8.2	16 — 6 readings
	0	8.0	17
	0	7.8	10
2:41	20		
2:42	20	18.5	13 — 3 readings
2:44	20	20.2	14 — 6 readings
2:45	20	20.3	13 — 3 readings
2:46	0		
2:47	0	7.8	15 — 5 readings
2:47½	30		
2:49	30	30.5	10 — 3 readings
2:50	30	33.1	13 — 2 readings
2:51	30	34.2	8 — 6 readings
2:52	0		
2:56	0	8.1	14 — 4 readings
2:59	"	7.8	23 — 3 readings
3:00	0	7.5	15 — 5 readings
3:00½	40		
3:02	40	21.8	16 — 2 readings
3:03	40	32.1	10 — 4 readings
3:04	40	37.8	15 — 3 readings
3:05	40	39.0	10 — 2 readings

The data presented in the two tables show that within the limits of the pressures that were studied the venous and capillary pressures are independent. A venous pressure ranging as high as 39 cm. of water may be accompanied by a low capillary pressure, and a low venous pressure may be associated with a high capillary pressure. In the experiment in which the venous pressure was artificially increased it was noted that while the blood pressure cuff was inflated, the color of the skin in the microscopic field assumed a dusky red color, but there was no engorgement of the visible capillaries.

These results are of considerable theoretic interest. They afford additional evidence of the functional independence of the capillaries. Since the venous pressure with a failing circulation rarely exceeds the figures noted in our observations, they give additional support to the

view that peripheral stasis is not conditioned by back pressure effects but rather by a lessened propelling force of the left ventricle. This diminished motive power of the heart results in a slowing of the blood stream, particularly in the peripheral vessels. A greater oxygen unsaturation of the capillary blood ensues, which is followed by a dilatation of the capillaries. Whether the dilatation is determined by the want of oxygen, by the absence of some hormone, as suggested by some of the work of Krogh, or by impaired nutrition of the capillary wall resulting from an inadequate blood flow, is unknown. Undoubtedly the dilated capillary walls are more permeable and at a certain stage of the process filtration edema will occur.

A number of physiologic observations seem to throw doubt on the correctness of our observations. The reports by earlier investigators can be ignored because their methods for the determination of capillary pressures were inaccurate. However, Danzer and Hooker [8] have noted an increase of from 2 to 3 mm. of mercury in the capillary pressure, induced by the Valsalva experiment, and an elevation of 2.5 mm. of mercury when a rubber band was loosely wound around the finger. We believe these changes of pressure are so small that they fall within the limits of error of the method employed.

More difficult to correlate with our findings are the observations of several authors that the blood pressure in any group of capillaries depends on their position in relation to the level of the heart. This is attributed to the hydrostatic pressure of the column of blood.[12] Thus Krogh reports that when the hand is lowered 29 cm. the capillary pressure rises 26.2 cm. of blood, which is equivalent to 20.2 mm. of mercury. Von Kries found that lowering the hand 28.5 cm. raised the capillary pressure by 11 cm. of blood or 8.1 mm. of mercury. Kylin, on the other hand, reports that lowering the hand 43 cm. raises the capillary pressure only 3.8 cm. of blood or 3 mm. of mercury. We have repeated these measurements and have found on one occasion that lowering the hand 37.5 cm. raised the capillary pressure 18.1 cm. of blood, or 14 mm. of mercury; on another, that a lowering of 41 cm. raised the capillary pressure 12.6 cm. of blood or 9.7 mm. of mercury.

Our findings lend themselves to several interpretations: First, that a venous pressure as high as 39 cm. of water may have no effect on the capillary pressure. Again, it may be that the failing driving power of the heart, on the one hand, and a reflex vasoconstriction from the inflation of the sphygmomanometer cuff, on the other, lower the capillary pressure enough so that the slight increase caused by the elevated venous pressure is not evident. For example, a patient may have a

12. Tigerstedt, R.: Die Physiologie des Kreislaufes, Berlin, **3**:274, 1922. Krogh, A.: The Anatomy and Physiology of Capillaries, New Haven, Yale University Press, 1922, p. 220.

capillary pressure of 20 mm. of mercury. With the failing propelling force of the heart, the capillary pressure may drop to 5 mm. of mercury. The heightened venous pressure may raise the capillary pressure by 5 mm., giving a resultant capillary pressure of 10 mm., which is lower than it was before myocardial insufficiency set in.

Either of these interpretations lead to the conclusion that the chief cause for peripheral stasis and edema lies in the weakened cardiac contraction and not in back pressure effects.

The only other explanation that suggests itself is that we have measured by the Danzer and Hooker method not the true capillary pressure but the pressure in the precapillary arterioles. The low capillary pressures found by Carrier and Rehberg [13] would point in this direction. On the other hand, the fact that we observed the effect of hydrostatic pressure on the readings makes us believe that we are dealing with real capillary pressures.

Whatever may be the final decision, the results obtained in this study give added significance to the high capillary pressures reported by one of us in certain cases of hypertension [10] and demonstrate conclusively that these high readings were not determined by a high venous pressure.

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13. Carrier, E. B., and Rehberg, P. B.: Capillary and Venous Pressures in Man, Skand. Arch. f. Physiol. **44**:20, 1923.

A STUDY OF THE MECHANISM OF ABSORPTION OF SUBSTANCES FROM THE NASOPHARYNX

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Two previous communications have indicated that the nasopharynx constitutes an area of peculiar physiologic significance. Observations on several cases of diabetes insipidus [1] uniformly showed that although the watery extract of the pituitary gland was not absorbed from any other internal or external surface of the body, it nevertheless gained rapid and effective entrance through the nasopharynx. The disclosure of such an interesting physiologic mechanism raised the query whether this absorptive power might extend also to particulate matter. Using the proper precautions to prevent absorption by any other route, it was found that particulate matter in the form of pulverized lead carbonate was readily absorbed from the upper air passage of cats and dogs.[2] The absorption was rapid and greatly in excess of the minimal toxic dose. Although these facts demonstrated that both solutions and particulate matter might eventually traverse the normal nasopharyngeal mucous membrane with readiness, they gave no clue to the underlying mechanism.

Search of the literature revealed scattered observations which, while not bearing directly on the point, are nevertheless suggestive in this connection. Since they have been uncovered in widely dissimilar investigative fields for the most diverse purposes, it would seem worth while to gather them together in this place in an effort to gain some insight into their possible relationship, and perhaps finally to gain some clue to the function of this important area.

PHENOMENA INDICATING ABSORPTION OF SUBSTANCES THROUGH THE NASOPHARYNX

Certain observations relating to the absorption of substances in the upper air passages are of considerable interest. Klebs [3] relates that it was an ancient custom among the Chinese and Hindus to vaccinate against smallpox by blowing the finely powdered virus into the nostrils. Similarly, Zerjgowsky [4] produced active immunity in animals by administering diphtheria toxin intranasally by sprays and cotton plugs.

1. Blumgart, H. L.: Antiduretic Effect of Pituitary Extract Applied Intranasally in a Case of Diabetes Insipidus, Arch. Int. Med. **29**:508 (April) 1922.
2. Blumgart, H. L.: Lead Studies VI, J. Indust. Hyg. **5**:153 (Sept.) 1923.
3. Klebs: Bull. Johns Hopkins Hosp. **24**:69, 1913.
4. Zerjgowsky: Ztschr. f. Immunitätsforsch., Abstr. **3**:602, 1910.

Blumenau [5] repeated these observations on large numbers of children, using intranasal plugs heavily soaked with undiluted toxin. Like Zerjgowsky, he found that the procedure caused no subjective symptoms, but was followed by the appearance of a small amount of antitoxin in the blood. These experiments der additional significance from the fact that Anderson [6] tried in vain to immunize guinea-pigs to diphtheria by subcutaneous injections of toxin.

More exact demonstration of absorption of substances by the nasopharynx is afforded by the experiments of Sewall [7] on guinea-pigs. He found that if 3 minims (0.18 c.c.) of horse serum were instilled intranasally into guinea-pigs, subsequent intravenous injections revealed that the animals had become either sensitized or immune. In the former group, the first intravenous injection caused speedy anaphylactic death. In the other group of animals, the first intravenous injection produced practically no reaction, and a second injection after an interval of three weeks was likewise withstood. Later work demonstrated that the transfer of immune serum conferred immunity on normal guinea-pigs, enabling the latter to withstand intravenous injections of horse serum which always proved fatal to controls. As the authors of these experiments realized, however, there was no assurance as to the site of absorption of the horse serum, since some may have reached the trachea and some was certainly swallowed.

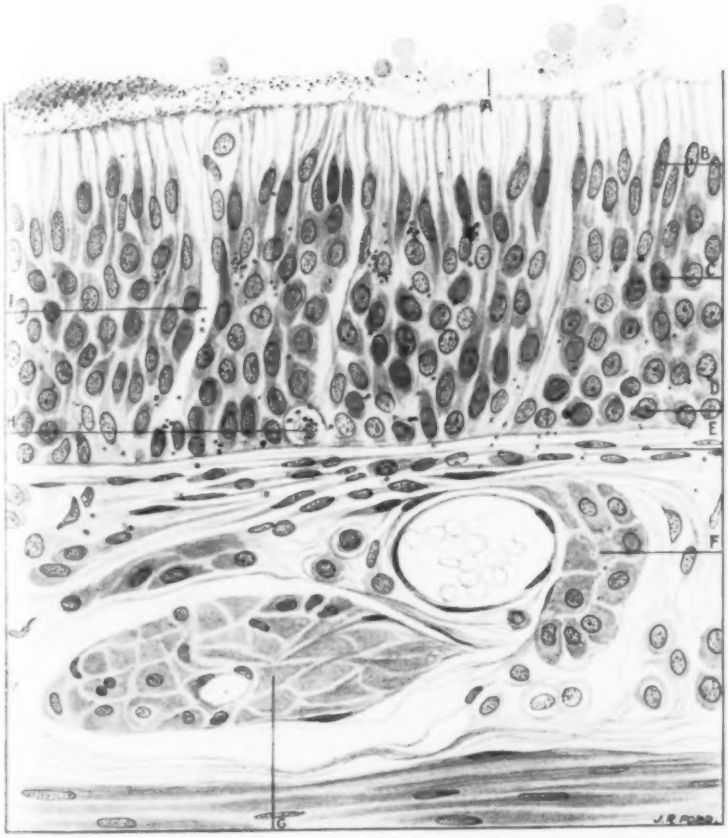
The only proof of absorption of substances actually in the nasopharynx is afforded by pituitary extract and lead carbonate. I demonstrated, in patients suffering from diabetes insipidus, that pituitary extract introduced intranasally effected a reduction in the fluid intake and urinary output entirely comparable in magnitude to hypodermic injections.[1]

To determine whether particulate matter might likewise be absorbed, cats and dogs were subjected to the following experiments: The esophagus was completely occluded by two or more ligatures, the trachea opened below the thyroid, and a tightly fitting glass cannula inserted. The lumen of the free upper end of the trachea was then occluded by two or more ligatures. Definite amounts of finely powdered white lead dust were then sprayed intranasally. After from eighteen to thirty-six hours, careful necropsies were made of the animals, the entire skin, and the head, trachea and esophagus above the ligatures discarded, and the skeleton and other tissues analyzed separately for lead. The average amount of lead recovered, expressed in terms of metallic lead, was approximately 22 mg. per animal. Although

5. Blumenau: Jahrb. f. Kinderh. **74**:141, 1911.

6. Anderson, J. F.: Hyg. Lab. Bull. 30, Washington, D. C., p. 906.

7. Sewall: Some Relations of the Brain and of the Olfactory Apparatus to the Process of Immunity, Arch. Int. Med. **13**:856 (June) 1914.



Camera lucida drawing of section of olfactory mucous membrane.

A indicates the cilia; *B*, zone of oval nuclei (sustentacular cells); *C*, zone of round nuclei (olfactory cells); *D*, basal cells; *E*, tunica propria; *F*, olfactory gland; *G*, cross section of nerve; *H*, small lymphatic; *I*, duct of olfactory gland.

the average weight of the animals was approximately one-fifteenth that of a 60 kg. man, the amount absorbed by each animal was more than twenty-two times the minimal toxic dose for a human being.

ENTRANCE OF PATHOGENIC ORGANISMS BY WAY OF THE NASOPHARYNGEAL MUCOUS MEMBRANE

The anatomic proximity of the nasopharynx to the cranial cavity and the appearance of signs of local meningeal irritation before the manifestation of generalized invasion have naturally stimulated workers to establish an etiologic relationship. Perhaps the most incisive experimental investigations relating to the nasopharynx have been undertaken in connection with anterior poliomyelitis and cerebrospinal meningitis. Strumpell [8] first advanced the hypothesis that the virus of poliomyelitis may reach the central nervous system by traveling along the olfactory nerves, an hypothesis which was established as fact by the researches of Flexner [9] and his co-workers. They found "that the virus passes with readiness and constancy from the intact or practically intact mucous membrane of the nose to the central nervous system and that this membrane, next to direct intracerebral introduction of the virus, gives the readiest method of successful inoculation." Flexner and Clark [10] showed that forty-eight hours after intranasal inoculation the virus could be demonstrated in the olfactory lobes of a monkey, whereas none could be demonstrated in the medulla or spinal cord. Additional evidence of the predilection of the virus of poliomyelitis to pass directly from the nasopharynx to the tissues of the central nervous system without previous hemic invasion was afforded by Clark, Fraser and Amoss.[11] They found that 10 c.c. of active poliomyelitis virus could be given to a monkey intravenously without causing the disease, whereas 0.2 c.c. or less of the virus, when injected intracerebrally, precipitated the characteristic train of symptoms. Furthermore, when the blood serum of the animals that received the intravenous injections was injected intracerebrally, the typical train of symptoms ensued.

The importance of the nasopharynx has likewise been emphasized by the study of cerebrospinal meningitis. Extensive clinical investigations have confirmed Flexner's [12] experimental observations that the meningococcus both enters and leaves the body by way of the mucous membrane of the upper part of the nasopharynx and the posterior nares. Opinion is divided, however, on the question whether the

8. Strumpell: Deutsch. Arch. f. klin. Med. 1891, p. 47.
9. Flexner, S.: The Mode of Infection in Epidemic Poliomyelitis, J. A. M. A. **59**:1371 (Oct. 12) 1912.
10. Flexner and Clark: Proc. Soc. Exper. Biol. & Med. **10**:1, 1912-1913.
11. Clark, Fraser and Amoss: J. Exper. Med. **19**:223, 1917.
12. Flexner, S.: Epidemic Meningitis, J. A. M. A. **69**:639 (Aug. 25) 1917.

organism passes directly to the central nervous tissues by way of the lymph spaces about the olfactory nerves, or indirectly by way of the blood. Early positive blood cultures, and the occurrence of metastatic meningococcal inflammation in the joints and the heart indicate that, at least in certain cases, the latter possibility prevails.

THE ANATOMIC RELATIONSHIP OF THE NASOPHARYNX

Schwalbe,[13] and later, Key and Retzius,[14] demonstrated by skilful postmortem injections the lymphatic connection between the subarachnoid space and the lymphatics of the nasal mucosa. As they utilized rather high injection pressures in dead and consequently less resistant tissues, there was no assurance that the path they demonstrated actually obtained during life. Weed's [15] admirable work, however, yielded more reliable data. He utilized subarachnoid injections of potassium ferrocyanid with postmortem fixation and precipitation by formaldehyd and hydrochloric acid. The pressures used "were slightly above normal and over considerable periods of time." Under these conditions, he found the granules of Prussian blue in the arachnoid cul-de-sacs above the cribriform plate, in the perineural spaces along the olfactory nerves as far as the nasal mucous membrane, where they lay beneath the surface in the meshes of loose connective tissue. He believed that these histologic findings indicated an accessory path of drainage for the cerebrospinal fluid and that from the loose tissue spaces it passed into the lymphatic vessels of the nasopharynx.

Although these studies show that a pathway exists between the subarachnoid space and the lymphatic spaces beneath the nasal mucous membrane, they shed no light on the mechanism or path by which substances may enter the body by traversing the mucous membrane of the nasopharynx. In view of the importance of this route in the conditions cited above, and in view of the susceptibility of this problem to experimental attack, the following work was undertaken.

OBSERVATIONS

1.. *The Absorption of Fluids.*—A. Crystalloids: In deciding what solution would yield the most trustworthy results, it seemed essential that the substance must satisfy certain experimental conditions.

1. The solution must be nontoxic. If the substance to be used were to traumatize the mucous membrane, there would be no assurance

13. Schwalbe: Centralbl. f. med. Wissensch. **7**:465, 1869.
14. Key and Retzius: Anatomie des Nervensystems u. d. Bindesgewebes, Stockholm, 1876.
15. Weed: J. Med. Res. **31**:21 (Sept.) 1914.

that the path traversed would be the path traversed under physiologic circumstances. The circulatory alteration that such traumatization would evoke, as well as the presence of agonal and necrotic cells, would inevitably distort the final picture.

2. The solution must not act as a tissue stain. Obviously, if the tissues tended to absorb this solution as a selective tissue stain, the presence of the substance intracellularly might merely represent a chemical combination rather than the course of a similar solution during life as it passed through the tissues of the mucous membrane.

3. The solution must be identified with certainty and be unaffected by the ordinary reagents used in preparing histologic sections.

The use of equal parts of potassium ferrocyanid and iron ammonium citrate as satisfying these conditions was suggested by the work of Weed on the cerebrospinal circulation. In none of his extensive series of researches did he find that injections of the substance acted as a tissue stain, notwithstanding the fact that the solution was injected into the subarachnoid space. "The precipitated granules were uniformly found clinging to the superficial portions of the cells and not within the cell bodies." Only in certain locations, such as in the arachnoid villi, did he find the granules intracellularly, and in this instance there was excellent reason to believe that it represented the true course of the fluid through a living semipermeable membrane. In all of Weed's experiments, the 2 per cent cent. solutions were injected directly into the spinal canal for periods of many hours' duration, without any phenomena indicating toxicity being observed. This is the more significant on account of the enormous accentuation of toxicity drugs manifest on intraspinous injection as compared to subcutaneous or even intravenous injections.

In the experiments described in this paper, it was found that such weak solutions underwent dilution in the nasopharyngeal mucus and were not as satisfactory as stronger concentrations of 15 or 20 per cent. Cats were the animals used. The solution was sprayed by means of an ordinary atomizer, care being taken to reach all possible portions of the anterior and posterior nares. The spraying was repeated at fifteen minutes intervals and the animals sacrificed after from one to six sprayings. The animals were killed with coal gas, a method which has been found to be speedy and painless and to involve a minimum of circulatory alteration.

As soon as respiration ceased, the animals were rapidly decapitated, the skin removed, the skull trephined in several places in order to facilitate fixation, and the tissues fixed in 10 per cent. solution of formaldehyd and 5 per cent. concentrated hydrochloric acid. The course of a

typical experiment, characteristic of others in this series, can be best illustrated by the following protocol:

Cat. Young adult. Solution of potassium ferrocyanid and iron ammonium citrate equal parts used. Strength of solution 20 per cent. Ten cubic centimeters sprayed intranasally using ordinary atomizer distributed at fifteen minute intervals over a period of two hours, i. e., 10:00 a. m., 10:15 a. m., 10:30 a. m., 10:45 a. m., 11:00 a. m., 11:15 a. m., 11:30 a. m., 11:45 a. m. and 12:00. At 12:15 animal placed in gas chamber and gas turned on. At 12:17 the cat was dead. The animal was immediately decapitated at the level of the fifth cervical vertebra, the skin removed and discarded, the head trephined, and the head and neck structures plunged into solution of formaldehyd 10 per cent. concentrated hydrochloric acid 5 per cent. at 12:21. Solution changed daily. On the third day dissection showed macroscopic blue coloration of the retropharyngeal lymph chain. Sections of the anterior nares, of the olfactory regions, tongue and oropharynx were dehydrated in graded alcohol, embedded in paraffin, counterstained with safranin and also with hematoxylin and van Gieson's stain. The sections were then mounted.

Microscopic examination of the sections of the tongue, anterior nares, and oropharynx showed a superficial deposit of the characteristic blue granular precipitate, but no evidence of any intracellular or intercellular penetration. The sections of the olfactory region presented a distinctly different picture as olfactory nerve cells showed distinct blue granules in their cytoplasm and along the periphery. The olfactory cells were bipolar, spindle shaped and contained round nuclei. These nuclei lay deep in the mucous membrane in contrast to the small, pyramidal, basal cells which formed the deepest nuclear zone, and the sustentacular cells which formed the more superficial nuclear zone. The peripheral processes of the olfactory cells were short and penetrated to the surface where they ended in a projecting tuft of hairline cilia. The basal cells and the sustentacular epithelial cells failed to show any blue granular content. There were characteristic granules in the loose connective tissue meshwork of the tunica propria, as well as in the lumens of some of the thin walled lymphatic vessels. Particular search of the nerves failed to reveal any evidence of absorption along such routes.

Control Experiment.—The animal was placed in the gas chamber at 2:50 p. m. It was dead at 2:55 p. m. It was decapitated. The nasopharynx was then sprayed with 5 c.c. of solution as above. The head was plunged into 10 per cent. solution of formaldehyd and 5 per cent. hydrochloric acid at 3:02. The tissues were prepared and examined as above. In all sections, deposition superficially of granular precipitate could be seen but no evidence of intercellular or intracellular absorption or staining.

Colloids: In order to ascertain whether colloids were absorbed by the same mechanism, a 5 per cent. solution of colloidal silver was sprayed intranasally at fifteen minute intervals for two hours. The tissues were prepared and examined in the usual way. No macroscopic evidence of absorption was visible. Microscopically, the tissues of the olfactory region again were the sole ones that showed evidences of penetration, the distribution being similar to that noted with potassium ferrocyanid although the concentration seemed in general somewhat less.

2. *Particulate Matter.*—(*a*) Ivory Black: To determine whether particulate matter traverses the nasal mucosa, experiments similar to the foregoing were performed, ivory black being insufflated in the dry powdered state. The substance consisted of particles of varying size, that is, from particles at the lower limits of vision to those about one quarter the size of an ordinary human red blood corpuscle.

After eight insufflations of this inert substance at fifteen minute intervals, the animal was killed as in the preceding experiments and the tissues examined.

Macroscopically, there were no significant findings. Microscopically, an occasional minute granule was to be seen on the periphery of an olfactory nerve cell or in the loose mesh work of the tunica propria.

(b) Fixed Staphylococcus aureus: To ascertain whether larger particles such as fixed organisms are absorbed through the nasal mucous membrane, cultures of *Staphylococcus aureus* were taken, washed and fixed in solution of formaldehyd. The organisms were then stained for four days in the cold with Ehrlich's acid hematoxylin. The suspension was then washed repeatedly in successive washings of distilled water until the supernatant fluid showed no sign of coloration. One cat was given eight insufflations of the suspension of organisms and then killed, another after similar treatment was killed after twenty-four hours. None of the tissues examined gave macroscopic or microscopic evidence of absorption of the organisms.

In order to obtain some index of the relative ease with which crystalloids and colloids are absorbed the following experiment was undertaken:

Cats were anesthetized with urethane subcutaneously. The trachea was identified and severed, the upper end occluded, and the lower end attached to a tracheal cannula. The esophagus was also identified and ligatured. A tightly fitting postnasal plug was introduced into the postnasal space in order to isolate the nasopharyngeal cavity. A cannula was introduced into the bladder so as to include within its lips the orifices of both ureters. A standard solution of phenolsulphonephthalein was then prepared of such strength that 1 c.c. contained 6 mg. At 12:02, 1 c.c. was sprayed intranasally. At 12:12, the urine issuing from the cannula became definitely pink, as it was caught in a test tube containing sodium hydroxid. At 1:42, 1 c.c. of the standard solution was given intravenously. The first marked change in the color of the urine was noted at 1:47.

One c.c. of a 5 per cent. solution of potassium iodid was similarly introduced, but no positive test was secured until one and a half hours had elapsed. The test used was the sodium nitrate and sulphuric acid test which was found sensitive to 1 minim (0.06 c.c.) of a 1:4,000 solution of potassium iodid that is, approximately 0.00002 gm.

In animals similarly prepared, 1 c.c. of phenolsulphonephthalein given orally appeared in a quantity to give color reaction only after from one-half to one hour.

COMMENT

The granules of potassium ferrocyanid, the molecules of colloidal silver, and the small particles of ivory black found in the tissues may safely be assumed to represent the true physiologic course of solutions as they traverse the mucous membrane of the nasal cavity. In the case of the potassium ferrocyanid precipitate, the control experiments eliminate the possibility of the potassium ferrocyanid-iron ammonium citrate solution having entered the cell by virtue of its chemical properties. Were the phenomena witnessed an expression of such staining, one would expect it to be diffuse and relatively uniform. These observations are in accord with the more extensive experience of Weed,[15] as recorded in his researches on the cerebrospinal circulation.

These experiments therefore indicate that solutions both crystalloid and colloid may pass by way of the olfactory receptor nerve cells into the lymphatic meshwork beneath the nasal mucous membrane and thence

to the retropharyngeal lymph nodes. A similar path seems to be traversed successfully by occasional minute particles of an inert substance such as ivory black. The path along the peripheral portions of the cell may well be analogous to the distinct spaces that Mott [16] has demonstrated about the capillaries and about each nerve cell in the brains of animals with experimental anemia. In view of the difficulty with which inert particles have been found to traverse the nasal mucous membrane, the relatively large amount of lead found deposited in the tissues of animals in previous experiments must receive one of two explanations: Either the lead carbonate was first dissolved in the mucus and then absorbed as a true solution, or the toxic action of the lead rendered the mucous membrane more permeable to the passage of particles of lead carbonate. It is, of course, entirely possible that both factors tended to operate.

It should be noted that the absorption of substances is accomplished only by those cells which conform to the description of the olfactory nerve cells. The observation of such absorption only in that area which conforms to the anatomic distribution of the olfactory nerve cells is confirmatory evidence. In view of this fact, the unique ability of the nasopharynx to absorb such substances as pituitary extract becomes correlated with the equally singular anatomic structure of the nasal olfactory mucous membrane. As Schaeffer [17] remarks:

> The cells that retain the olfactory characteristics and functions are known as neuroblasts. They remain in the walls of the nasal pits, become bipolar olfactory cells and by central processes become connected with the brain. They represent morphologically the ganglionic cells in the dorsal (sensory) roots of the spinal nerves, and retain the primitive location of such sensory cells in the surface epithelium. The olfactory cells are unique in this regard among neuro-epithelial elements.

The failure of previously fixed organisms to be absorbed in the foregoing experiments is not surprising, for under the conditions they represent merely inert particles of relatively large dimensions. No analogy can be drawn between the fate of such inert particles and living organisms. The question as to whether the virus of poliomyelitis and the meningococcus utilize the same pathway as the true solutions in these experiments, is of considerable interest. All clinical and experimental observations evidently agree that the precise site of election of both organisms is over the olfactory mucous membrane, exactly that area through which substances have been shown to pass in these experiments. Even if one assumes the course of infection in these diseases to be that detailed above, the exact pathway from the lymphatics of

16. Mott: Lancet, Pt. 2, 1 and 79 (July 2 and 9) 1910.

17. Schaeffer: The Nose, Paranasal Sinuses, Nasolacrinal Passages, and Olfactory Organs, in Man, Philadelphia, P. Blakiston's Son & Co., 1920, p. 267.

the tunica propria to the tissues of the central nervous system is not yet absolutely clear. According to the researches of Weed, the normal path of cerebrospinal fluid drainage is from the subarachnoid space along the perineural spaces of the olfactory nerves outward into the loose meshwork of lymphatic spaces of the submucosa. The absence of granules in the perineural spaces in the experiments presented after intranasal spraying of potassium ferrocyanid are in accord with Weed's experiments; for, were the direction of flow from the periphery toward the subarachnoid space, one would have expected to find granules along this route. It must be remembered, however, that in these locations we are dealing with extremely small differences of pressures such as would readily permit reversals of current. That such reversals may actually occur is suggested by certain experimental considerations. Weed [18] found that if lumbar puncture was performed on monkeys soon after the intravenous injection of a dose of *Bacillus mucosus-capsulatus,* fatal meningitis ensued, whereas in a series of controls in which lumbar puncture was not performed, double the intravenous dose was not attended by any such consequence. The ascending course of tetanus toxin along the nerves is also exceedingly suggestive in this connection, especially since it has been demonstrated that the perineural spaces of such nerves likewise constitute an accessory path of cerebrospinal fluid drainage. The admirable studies of Friedenwald [19] in the virus of herpes simplex also bear on this point. He found that after a rabbit had received a corneal inoculation of herpes simplex, the virus could be transmitted from rabbit to rabbit with the production of typical lesions by removing the gasserian ganglion, emulsifying it in saline and inoculating it into the cornea. Every such gasserian ganglion examined microscopically showed definite lesions not found in the normal controls. Similarly, Flexner and Lewis [20] have shown that the virus of poliomyelitis will travel up the sheath of the sciatic nerve affecting first that side of the cord on which the injection was made. The final evidence that such reversals of current do occur is afforded by Weed's [21] recent experiments, in which he studied the paths of drainage after intravenous injections of hypertonic solutions.

It would seem that any such striking property as has been shown to exist in the olfactory cells might well be related to their chief function. In connection with the ability of these cells to transmit solutions, it is

18. Weed: Production of Meningitis by Release of Cerebrospinal Fluid, J. A. M. A. **72**:190 (Jan. 18) 1919.

19. Friedenwald: Arch. Ophth. **53**:105 (Feb.) 1923.

20. Flexner, S., and Lewis, P. A.: The Transmission of Epidemic Poliomyelitis to Monkeys, J. A. M. A. **53**:1913 (Dec. 4) 1909.

21. Weed: Am. J. Anat. **31**:3 (Jan.) 1923.

interesting to quote Parker [22] to the effect that "the adequate olfactory stimulus for both water inhabiting and air inhabiting vertebrates is a solution in contact with the olfactory hairs and perhaps formed in part within these bodies" (p. 81). That such solutions are in an eminently favorable situation to act chemically on the olfactory receptors is indicated by these experiments.

The presence of an area of such unique absorptive power naturally excites curiosity as to whether it may play some other rôle in addition to its possible importance in olfaction. The work of Sewall, previously cited, strongly suggests that nasopharyngeal absorption may play an important rôle in establishing resistance to the "droplet infections." The anatomic design of the upper respiratory passages which serve to prevent the progress of particles to the more vulnerable pulmonary passages, the power of mucus to dissolve organisms and the ability of the nasopharynx to absorb such decomposition products and transmit them to the underlying lymphatics constitute a chain of forces splendidly adapted to the creation of natural active immunity.

SUMMARY AND CONCLUSIONS

1. Previous observations, clinical and experimental, demonstrated that the nasopharynx constitutes an area of singular absorption.

2. The experiments here presented indicate that crystalloids, colloids and, to a lesser extent, particulate matter, traverse the nasopharyngeal mucous membrane by being absorbed by way of the olfactory nerve cells and thence to the systemic lymphatics.

3. The clinical and physiologic significance of these findings is discussed.

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22. Parker: Smell, Taste and Allied Senses in Vertebrates, Philadelphia, J. B. Lippincott Co., 1922.

OBSERVATIONS ON A GROUP OF MARATHON RUNNERS

WITH SPECIAL REFERENCE TO THE CIRCULATION *

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PART I. THE VITAL CAPACITY OF THE LUNGS BEFORE AND AFTER A MARATHON RACE

The American marathon race takes place annually in Boston on April 19. Generally, the men who participate in this 25 mile race are the best long distance runners in the United States and Canada. It, therefore, seemed to be an exceptional opportunity to observe the effect of prolonged vigorous training and a strenuous prolonged effort on certain features of the circulation. The first part of the paper deals with observations on the vital capacity of the lungs, the second with the size of the heart as determined by roentgenograms and the third with some miscellaneous notes, such as the blood pressure and general condition of the runners.

Most observers who have studied the vital capacity of the lungs in health and disease have noted that some of those better trained attained abnormally high figures. With this in mind, determinations of all the participants in the American marathon race were made just before the race. These men had all been training for some months immediately preceding the race, and most of them had been doing long distance running for from five to fifteen or more years. It is fair to say that such a group of men should show the effect of prolonged vigorous training, as running ten or more miles repeatedly and frequently under the pressure of competition year in and year out should test or develop the circulatory mechanism to a maximum.

One must immediately ask which method should be used in determining the percentage of the normal vital capacity. Are the figures to be calculated on a height basis or by the surface area method? Peabody,[1] in his early work, originally made three groups, depending on the height, but soon it was appreciated that important errors resulted when the shorter and taller members of each group were compared to the same standard. Obviously, it would have been more satisfactory if average normal figures had been available for each centimeter of

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1. Peabody, F. W., and Wentworth, J. A.: Clinical Studies on Respiration, Arch. Int. Med. **20**:433, 443 and 468 (Sept.) 1917.

height. The small number of observations of Peabody's series did not permit this. Subsequently, West [2] made calculations using the surface area as his basis, and he thought that for males, the normal vital capacity in liters should be 2.5 times the surface area in square meters. This assumes that the vital capacity of the lungs is a function of the surface area. This, it seems, is not necessarily true from either a theoretical or practical standpoint. However, for persons of normal weight, it probably would work out satisfactorily. More recently, Hewlett and Jackson [3] made charts of a large series of young adult males and concluded that the vital capacity was a simple function of the height, that is the vital capacity in cubic centimeters was 50 and the height in centimeters, 4,400. This means that the taller the person, the greater will be the vital capacity, and the graph when plotted will be a straight line and each increment in height will have the same increase in vital capacity.

In Table 1 are charted all the readings made in this study. The actual vital capacities obtained before the race are noted; then the calculated normal figure follows determined from the surface area, and then the percentage of normal. For purposes of comparison, a further calculation is made on the basis of height. There are apparent wide variations in the different runners. On the basis of surface area, the lowest figure is 71 per cent. and the highest 138 per cent., and on the basis of height the lowest is 76 per cent. and the highest 138 per cent. The average of the two methods is 98.6 per cent. using the surface area and 103.3 per cent. using the height standard. This indicates that even the most extreme kind of training probably has little influence, if any, on the vital capacity of the lungs, for certainly the general average of so large a group would have reflected the results of training by a figure approximately from 15 to 20 per cent. above the normal. There were nine men with figures more than 15 per cent. below normal, using the surface area method, and four using the height method. There were only three more than 15 per cent. above normal with the former method and ten with the latter. One is struck by the fact that the vital capacities varied a great deal from below normal to above normal and that there was no important relation between the vital capacity of the lungs and the order in which the runners finished.

Observations were made on twenty of the runners a few minutes after they finished the race. They were quite exhausted and fatigued, although they made a strenuous effort in blowing. The vital capacity

2. West, H. F.: Clinical Studies on Respiration; Comparison of Various Standards for Normal Vital Capacity of Lungs, Arch. Int. Med. **25**:306 (March) 1920.

3. Hewlett, A. W., and Jackson, N. R.: Vital Capacity in a Group of College Students, Arch. Int. Med. **29**:515 (April) 1922.

TABLE 1.—*Vital Capacity Readings* *

Running Number	Height	Weight	Surface Area	Normal Vital Capacity Calculated from Surface Area	Vital Capacity Before Race	Percentage of Normal	Vital Capacity After Race	Time After Finish	Percentage of Fall of Vital Capacity After Race	Vital Capacity Calculated from Height§	Percentage of Normal
63	173	62.8	1.76	4.40	5.20	118	4.10	6 min.	21	4.25	122
							5.20	30 hrs.	0		
26	175	67.6	1.82	4.55	4.75	104	....	.....	..	4.35	109
55	164	55.4	1.60	4.00	4.40	110	....	.....	..	3.80	116
70	170	60.4	1.70	4.25	4.25	100	3.95	9 min.	7	4.10	104
40	172	57.6	1.68	4.20	3.90	93	3.50	5 min.	10	4.20	93
41	167	59.8	1.68	4.20	3.70	88	2.95	7 min.	20	3.95	94
59	172	61.2	1.72	4.30	3.95	92	....	.....	..	4.20	94
22	172	61.8	1.74	4.35	4.70	108	4.55	6 min.	3	4.20	112
18	158	51.2	1.50	3.75	3.90	104	3.40	3 min.	13	3.50	112
44	172	63.0	1.76	4.40	4.65	106	....	.....	..	4.20	111
74	177	54.6	1.66	4.15	4.30	104	3.40	3 min.	21	4.45	97
53	167	52.2	1.58	3.95	4.30	109	3.45	4 min.	20	3.95	109
50	172	61.6	1.74	4.35	4.60	106	....	.....	..	4.20	110
57	170	65.4	1.76	4.40	3.85	88	2.95	4 min.	23	4.10	94
13	160	57.6	1.60	4.00	3.65	91	....	.....	..	3.60	101
23	162	57.6	1.62	4.05	3.35	83	2.80	3 min.	16	3.70	91
21	162	53.0	1.56	3.90	4.30	108	3.80	1 min.	10	3.70	114
7	175	60.4	1.74	4.35	4.95	114	4.45	6 min.	10	4.35	114
37	165	61.4	1.68	4.20	4.80	114	3.60	3 min.	25	3.85	125
52	165	69.4	1.76	4.40	4.15	95	2.00	4 min.	52	3.85	108
19	178	57.2	1.72	4.30	4.50	105	....	.....	..	4.50	100
45	170	63.0	1.74	4.35	4.35	87	3.05	2 min.	20	4.10	93
65	160	61.4	1.64	4.10	4.10	84	3.25	2 min.	6	3.60	96
58	167	55.0	1.62	4.05	3.80	94	....	.....	..	3.95	96
31	170	65.0	1.70	4.40	3.10	71	2.70	2 min.	13	4.10	76
2	175	60.8	1.74	4.35	6.00	138	4.60	3 min.	23	4.35	138
							6.00	22 hrs.	0		
29	177	59.0	1.74	4.35	3.95	91	....	.....	..	4.45	89
49	180	68.5	1.88	4.70	5.15	110	4.55	2 min.	11	4.60	112
10	177	71.6	1.88	4.70	5.50	117	....	.....	..	4.35	126
32	165	55.8	1.62	4.05	4.50	111	....	.....	..	3.85	117
6	167	54.4	1.60	4.00	3.35	84	....	.....	..	3.95	85
17	177	74.0	1.90	4.75	5.20	110	....	.....	..	4.45	117
30	162	54.4	1.58	3.95	3.70	94	2.90	3 min.	21	3.70	100
4	172	66.6	1.80	4.50	3.95	88	....	.....	..	4.20	94
1	165	66.2	1.74	4.35	4.30	99	....	.....	..	3.85	112
8	170	61.2	1.70	4.25	4.50	106	....	.....	..	4.10	110
9	163	58.0	1.62	4.05	4.20	104	....	.....	..	3.75	112
12	160	60.0	1.62	4.05	4.20	104	....	.....	..	3.60	117
15	...	51 4	....	....	...	...	....	.....	..	....	...
14	170	52.6	1.60	4.00	3.30	83	....	.....	..	4.10	81
16	175	65.4	1.80	4.50	3.90	87	....	.....	..	4.35	90
17	167	61.8	1.70	4.25	3.35	79	....	.....	..	3.95	85
20	162	52.6	1.54	3.85	3.50	91	....	.....	..	3.70	95
24	...	58.6	....	....	3.30	...	....	.....	..	....	...
25	165	57.6	1.62	4.05	3.25	80	....	.....	..	3.85	85
27	172	64.4	1.76	4.40	4.00	91	....	.....	..	4.20	95
28	167	64.8	1.72	4.30	4.20	98	....	.....	..	3.95	106
30	180	54.8	1.70	4.25	4.45	105	....	.....	..	4.60	97
31	177	57.8	1.72	4.30	4.00	93	....	.....	..	4.45	90
34	177	64.4	1.80	4.50	4.40	98	....	.....	..	4.45	99
35	177	78.6	1.96	4.90	3.70	76	....	.....	..	4.45	83
38	172	79.4	1.94	4.85	4.50	93	....	.....	..	4.20	107
41	170	57.6	1.66	4.15	3.40	82	....	.....	..	4.10	83
42	180	65.8	1.84	4.60	4.30	94	....	.....	..	4.60	94
43	170	61.2	1.70	4.25	4.90	115	....	.....	..	4.10	120
45	177	65.8	1.82	4.55	4.60	101	....	.....	..	4.45	103
54	182	74.4	1.90	4.90	4.80	98	....	.....	..	4.70	102
62	177	69.0	1.86	4.65	4.60	99	....	.....	..	4.45	103
66	178	65.4	1.82	4.55	5.05	111	....	.....	..	4.50	122
67	170	62.2	1.72	4.30	4.45	104	....	.....	..	4.10	109
68	177	69.4	1.86	4.65	4.65	100	....	.....	..	4.45	104
69	167	67.6	1.76	4.40	4.60	105	....	.....	..	3.95	116
71	175	63.2	1.78	4.45	4.90	110	....	.....	..	4.35	113
73	168	64.6	1.74	4.35	3.80	87	....	.....	..	4.00	95
75	166	60.4	1.68	4.20	4.10	98	....	.....	..	3.90	105
76	170	69.4	1.80	4.50	4.55	101	....	.....	..	4.10	111
78	162	66.0	1.74	4.35	4.10	94	....	.....	..	3.70	111

* Observations tabulated in the order of finish of the first thirty-four runners.
Height is expressed in centimeters; weight in kilograms; surface area in square meters and vital capacity in liters.
§ The height formula of Hewlett and Jackson, vital capacity = 50; height minus 4.400.

of the lungs in most of the cases fell appreciably. The average fall was 17 per cent., and the average time after the finish of the race that the observations were made was 3.8 minutes. This fall we believe is due to the physical exhaustion and less effective control of the respiratory muscles rather than to any impediment to the inflow of air into the lung spaces. The latter hypothesis is still possible, although no evidence of congestion of the lungs, such as râles at the bases, was made out on auscultation. In several instances, it was found that the vital capacity reading returned to the original figure a day or so after the race.

PART 2. THE EFFECT OF THE MARATHON RACE ON THE SIZE OF THE HEART

Many observations have been reported on the effect of long distance running or prolonged effort on the size of the heart, but probably because of the varied methods of study, the results have been conflicting. In 1899, Williams and Arnold [4] studied the hearts in competitors before and after the Ashland-Boston marathon race by means of palpation and percussion. For three successive years, Larrabee and Strong [5] observed runners who participated in this annual event. These findings were also based on changes in the percussion outline of the heart. They reported a general enlargement in nearly all competitors before the race with a further and more or less symmetrical increase immediately after the race.

In 1909, Boyce and Grier, under the direction of Watson L. Savage,[6] made fluoroscopic studies of hearts in competitors of the Pittsburgh marathon. The first observations after the effort were made from fifteen to sixty minutes after the completion of the race. Their findings suggested an enlargement immediately following the race, with a reduction in the heart outline one week later. They also concluded that the hearts of successful marathon runners were above the average size.

Boigey [7] made orthodiagraphic records of competitors before and after a 42 kilometer race and found dilatation of the heart. In the same paper, he noted a contraction of the heart after a 100 meter foot race. Dedickem [8] examined by palpation and percussion 226 runners before and after a 50 kilometer marathon. He was unable to demonstrate any enlargement of the heart.

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4. Williams and Arnold: Philadelphia M. J. **3**:1233, 1899.
5. Blake, J. B.; Larrabee, R. C., and Strong, L. W.: Boston M. & S. J. **148**: 201, 1903.
6. Savage, W. L.; Boyce, J. W., and Grier, G. W.: Am. Phys. Education Rev. **15**, No. 9 (Dec.) 1910; **16**, Nos. 1, 2, 3, 4, 5 (Jan., Feb., March, April, May) 1911.
7. Boigey: Presse méd. **26**:657, 1921.
8. Dedickem: Acta Med. Scand. **53**:738, 1921.

On various occasions, Shott [9] has contended that the heart dilated following exercise. In 1908, Moritz [10] found that the heart shadow, as seen by orthodiagram, failed to enlarge after exercise and that in certain instances, it contracted. This phenomenon was seen in normal and in slightly pathologic hearts. De la Camp [11] arrived at the same conclusions as did Hoffmann,[12] who reported that he was unable to determine any dilatation in the normal heart following exertion.

In 1914 Nicolai and Zuntz [13] studied the effect of exercise on the heart in normal subjects operating a tread-mill. They reported a transverse diameter increase during work and a decrease a few seconds after work. Williamson,[14] in 1915, studied most accurately the effect of stair climbing on the size of the normal and pathologic heart. He measured the transverse diameters on teleoroentgenograms and paid considerable attention to the position of the diaphragm. He was of the opinion that normal and about one half of the pathologic hearts diminished in size after exertion. In the same year, Lee, Dodd and Young [15] showed that there was little difference in the size of the hearts of men who had been rowing two or four years and men who had been rowing more than ten years. One of us, working with Strong,[16] studied the effects of exercise to exhaustion on the normal and abnormal rabbit's heart. The animals were exercised in a tread-mill and the heart size, as determined by the roentgen ray, before exertion was compared with the silhouettes taken at various times following exertion. In most instances, there was a definite decrease in size after effort not only of normal but also of pathologic hearts, and a gradual return to normal after one hour.

In this study of the Boston marathon of April, 1923, we used a standard portable roentgen-ray apparatus with an adjustable vertical plate holder.[17] The equipment was placed on the second floor of the Boston Athletic Association club rooms, close to the elevator and within

9. Shott, T.: Verhandlungen des Kongresses fur Innere Med. **9**:448, 1890; München. med. Wchnschr. **55**:952, 1908; Deutsch. med. Wchnschr. (April, 1897) p. 220.

10. Moritz, F.: München. med. Wchnschr. **55**:713 and 1331, 1908.

11. De la Camp: Ztschr. f. klin. Med. **51**:1, 1903.

12. Hoffmann, A.: Verhandlungen des Kongresses, f. Innere Med. **20**:307, 1902.

13. Nicolai, G. F., and Zuntz, N.: Berl. klin. Wchnschr. **51**:821, 1914.

14. Williamson, C. S.: Am. J. M. Sc. **149**:492, 1915.

15. Lee, R. I.; Dodd, W. J., and Young, E. L.: Boston M. & S. J. **173**:499, 1915.

16. Gordon, B., and Strong, G. F.: Studies on the Rabbit's Heart, Arch. Int. Med. **32**:510 and 517 (Oct.) 1923.

17. The films were taken at a distance of 3 feet and a current of 10 millimeters was used, backed up by a 4½-inch spark gap, with an exposure of five seconds. The equipment was supplied by Kehlenback and Saxby, agents for the Wappler Company in Boston.

100 yards of the finish line. A convenient dark room was at hand to facilitate the change of films. Our technic consisted of immediately bringing the runners from the street and having them stand in front of the plate holder. In some instances, the men were so completely exhausted that it was necessary to give them assistance in order to maintain an upright position during the procedure. Without delay, the picture was made, and in most instances the entire operation was completed within three minutes after the runner crossed the finish line. The competitors then rested for about one hour and returned to the stand for a second roentgen-ray film. A number of men came to the roentgen-ray department of the Peter Bent Brigham Hospital the next day or some days later, when other heart plates were taken. It was unfortunately impossible to obtain roentgenograms before the race for comparison, but this did not prevent certain obvious deductions from our studies.

The results are charted in the accompanying Table 2. It will be noticed that immediately after the race (Period A) all the hearts were rather small; none was dilated. In six cases examined from one to one and one-quarter hours later, the second roentgenogram (Period B) showed that the heart must have been contracted about 1 cm., for the transverse diameter in B was distinctly larger than in A. There were four other instances in which the change amounted to only a few millimeters, but these were considered to be within the limit of technical error. Further roentgen-ray data were obtained in five cases, from one to sixteen days after the race, for purposes of comparison (Period C). All of them showed a further increase over the dimensions obtained about one hour after the race, and one showed an increase of 1.1 cm. although none had been previously noted.

In this study, due consideration was given to the position of the diaphragm as suggested by Williamson,[14] Bordet,[18] and others. It is known that a high diaphragm produces an increased transverse diameter of the heart shadow for purely mechanical reasons. In Table 2 are charted six instances in which the position of the diaphragm was different in the various plates of the same person. In four of them, there was a gradual increase in the size of the heart after the first roentgenogram was taken. In two, there was no appreciable change. The increase occurred in three instances with the diaphragm lower (Nos. 63, 60, and 22) and in one with the diaphragm higher (No. 11). This indicates that despite the higher position of the diaphragm immediately after the race which might have increased the transverse diameter of

18. Bordet, E.: Arch. des mal. du coeur, February, 1923, p. 108.

the heart, apparently the hearts were smaller than they were later when the diaphragm descended; in a word, the position of the diaphragm did not alter the general deductions that might be drawn from these observations.

A further control on the roentgen-ray measurements appears in comparing the transverse diameter of the chest of the same persons in

TABLE 2.—*Roentgen-Ray Measurements of the Heart and Chest*

Running Number	Order of Finish	Time Elapsed Between Finish of Race and Taking of Roentgenograms	Transverse Diameter of Heart	Internal Transverse Diameter of Chest	Cardio-thoracic Ratio Percentage	Position of Diaphragm
63	1	A 1½ min.	12.5	32.9	38	—
		B 86 min.	13.3	32.5	41	Lower
		C 29 hrs.	14.0	34.5	41	Equal
26	2	A 2½ min.	13.2	32.0	41	Equal
		B 80 min.	14.2	32.1	44	
55	3	A 2 min.	11.5	31.4	36	—
70	4	A 1¼ min.	14.4	31.0	43	—
		B 87 min.	14.2	31.2	46	Higher
46	5	A 3½ min.	14.4	31.4	46	Equal
		B 88 min.	14.5	31.9	45	
44	6	A 5 min.	13.3	30.2	44	Equal
		B 63 min.	12.9	30.5	42	
39	7	A 5 min.	11.7	29.8	39	Equal
		B 60 min.	11.9	30.3	39	
22	8	A 2 min.	12.7	30.5	42	Equal
		B 73 min.	13.6	32.6	42	
		C 17 hrs.	14.4	34.5	42	Lower
18	9	A 4 min.	13.3	29.3	45	Equal
		B 62 min.	13.2	29.6	45	
74	11	A 2 min.	16.2	33.8	48	Equal
		B 64 min.	16.9	34.2	50	
36	12	A 2 min.	12.2	29.2	42	Equal
		B 65 min.	13.1	29.8	44	
		C 16 hrs.	15.6	29.5	53	
59	13	A 2¼ min.	13.1	33.5	39	Equal
		B 67 min.	13.2	34.7	38	
57	14	A 2¾ min.	13.0	32.4	40	—
15	15	A 2 min.	12.7	33.2	38	—
23	16	A 1¾ min.	12.6	30.4	41	—
		B 57 min.	12.6	30.4	41	Higher
7	18	A ¾ min.	14.2	32.1	44	Equal
		B 62 min.	14.4	32.5	44	
		C 16 days	15.5	32.0	36	
27	19	A 2 min.	12.3	31.1	40	Equal
		B 69 min.	13.8	31.6	44	
56	20	A 5 min.	12.7	33.7	38	—
60	23	A 2 min.	11.5	28.3	41	—
		B 70 min.	12.5	28.5	44	Lower
58	24	A 1¾ min.	10.9	30.3	36	—
11	25	A 3 min.	11.5	29.3	39	—
		B 60 min.	12.5	29.2	43	Higher
2	26	A 2 min.	12.7	32.3	39	Equal
		B 99 min.	13.7	32.2	42	
		C 18 hrs.	13.9	31.7	44	

different plates. With three exceptions, Nos. 22, 59, and 63, the difference was under 0.6 cm. This indicates that from a technical point of view the heart measurements were obtained with a satisfactory degree of accuracy. By dividing the transverse diameter of the heart by the internal transverse diameter of the chest, the so-called cardiothoracic

ratio may be obtained which, according to Danzer,[19] in normal people should not exceed 52 per cent. The figure is applicable only when obtained from a heart plate taken at a distance of 7 feet. Our readings were made from plates taken at a distance of 3 feet. One can readily see that the hearts were on the whole small or normal. Comparing the cardiothoracic ratio of roentgen-ray plates taken at 3 feet with those taken at 7 feet in a group of normal persons, we found that the former was 3 per cent. less than the latter; therefore, the upper limit of normal in our measurements would be 49 per cent. From our table, one may conclude that the marathon runners showed no enlargements of the hearts, for in only one instance (Runner 33) was the ratio appreciably above normal at any time.

PART 3. BLOOD PRESSURE AND GENERAL CONSIDERATIONS

Due to certain difficulties in the work, only a limited number of blood pressure measurements were made. The pressure was taken either on the right or left brachial artery by means of a Tycos manometer, with a cuff 12 cm. broad. The reading was made on decreasing contrapressure. The systolic pressure was easily determined, while the diastolic was difficult to obtain, because the sounds were of decreasing intensity before the diastolic contrapressure was reached and were present a long time in the infradiastolic zone; thus the characteristic feature of the changing quality of the sound was not easily ascertained. This refers to the readings made by the auscultatory method. There were almost similar features to deal with in the use of the palpatory method, the thumb palpating the brachial artery just below the armlet. In the present observations, both methods were employed simultaneously, and often the doubt resulting from one was cleared up by employing the other. Furthermore, in some instances, we were helped by observing the oscillations of the small spring manometer, thus making use, in a rough way, of the oscillatory method. In a few cases, however, no definite figure could be ascertained.

We never found a so-called "gap" or even a "valley" in the infrasystolic zone. The intensity of the arterial sounds increased progressively, and this, according to the recent work of Barbier[20] indicates an energetic expulsion of the blood throughout the cardiac systole. The loud blowing character of the arterial sound that was found in the infrasystolic zone and the increased resonance of the sounds around and above the diastolic point, are, according to the same author, the result of a hypertonic state of the arterial wall (vasoconstriction, hypersympatheticotonus); but they can also be due, at least partially, to increased pulse pressure.

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19. Danzer, C. S.: Am. J. M. Sc. **157**:513, 1919.
20. Barbier, J.: La methode auscultatoire dans l'exploration cardiovasculaire, Thèse, Lyon, 1921.

The blood pressure readings are given in Table 3. In most instances, immediately after the race, the systolic pressure was found to be about normal; on the other hand, the diastolic pressure was definitely reduced, the ratio, of systolic to diastolic, which ranges normally from 1.4 to 1.7, being thus increased. During the following hours, it seems that first the systolic pressure fell and then both the systolic and diastolic rose together to normal. It is quite apparent that our data are incomplete concerning blood pressure changes. This subject and observations on the tonus of the blood vessels need further investigation.

We had occasion to talk with the men during the examination (or at a later date) about the symptoms they experienced during the race. Quite a number remarked about the pain in the upper part of the

TABLE 3.—*Blood Pressure Examinations*

Running Number	Arrival Number	Blood Pressure (in Mm. of Mercury) Up to 10 Min. After the Finish			Blood Pressure (in Mm. of Mercury) At Varying Times After the Race		
		Maximum	Minimum	Time	Maximum	Minimum	Time
63	1	110	58	4 min.	118	72	30 hours
46	5	130	70	9 min.	—	—	—
22	8	—	—	—	148*	92*	1 hr. 40 min.
18	9	—	—	—	108	58	1 hr. 30 min.
40	10	130	58	8 min.	—	—	—
20	13	—	—	—	98	72	1 hr. 15 min.
57	14	134	70 or 50	7 min.	—	—	—
53	20	110	84	8 min.	—	—	—
48	22	130	54	8 min.	—	—	—
60	23	132	80	5 min.	—	—	—
2	26	150	66	7 min.	126	86	22 hours
19	29	120	58	10 min.	—	—	—
52	30	—	—	—	92	62	45 minutes
					102	82	1 hr. 10 min.
77	32	120	78 or 58	9 min.	—	—	—
25	—	108	58	—	—	—	—
8	—	112	60 ?	—	106	78	45 minutes
54	—	130	88	—	—	—	—

* Runner 37 years old.

right side of the abdomen which appeared after the first two or three miles. Others referred to a slight nausea that came later in the race. These discomforts usually disappeared after slowing the speed or walking for a short distance. Most of the men at some time or another experienced pain or stiffness in the muscles of the legs and blisters on the soles of the feet. They felt that their position at the finish line depended largely on the condition of their legs and that all other discomforts were of minor importance. None complained of any difficulty in breathing or pain in the chest. When asked why they could not run faster at the end of the race, they all said that their "legs just would not move any faster." They insisted that dizziness did not enter into it.

On examination, no râles were heard in the lungs, and the liver edge could not be felt. It was thought that one of these positive findings might be present as evidence of circulatory embarrassment, but on

considering the entire picture that a marathon runner presents, we came to the conclusion that given a normal heart, the most important point in summary training is that of the legs rather than the wind.

SUMMARY

1. The average vital capacity of the lungs in marathon runners was normal, which indicated that prolonged vigorous training did not increase the breathing space of the lungs.

2. There was a fall of 17 per cent. in the vital capacity immediately following the race, and this returned to normal in twenty-four hours.

3. There was no important relationship between the vital capacity of the lungs and the order in which the runners finished.

4. The size of the heart as determined by the roentgen ray in marathon runners is not enlarged. This indicated that many years of the most vigorous physical effort did not produce cardiac hypertrophy.

5. Immediately following the race, it seems that there was a temporary decrease in heart size, gradually returning to normal in about one day.

6. No "gap" was found in the auscultatory curve of the brachial artery. The systolic pressure immediately after the race was normal while the diastolic was distinctly diminished. It is suggested that shortly afterward the systolic pressure fell, whereupon both pressures slowly rose to normal.

GASTRIC SECRETION, GASTRO-INTESTINAL MOTILITY AND POSITION OF THE STOMACH

IN A GROUP OF 250 CHILDREN OF THE LYMANHURST SCHOOL

C. B. WRIGHT, M.D.

MINNEAPOLIS

There is a large amount of literature on the position of the stomach in the adult and in the suckling, but not so much on its position in older children. Previous to the use of the roentgen ray and the opaque meal much work was done by percussion and air or gas distention on the cadaver, but with the use of the roentgen ray it was found that these observations did not give us an accurate knowledge of the position of the stomach and colon in the living upright person, and from the clinical standpoint; this, of course, is the important consideration.

DeBuys and Henrique,[1] in a study of infants and young children, did not find an adult type of stomach up to the age of 3 years. They also first noted active peristaltic waves in the stomach of a child at the age of 4 months. Petri,[2] in a series of observations on fourteen infants' stomachs, found that although the major portion of the meal passed into the intestines in from one and a half to two and a half hours, the stomach did not completely empty until from four to seven hours. Richard R. Smith[3] examined 109 female children varying in age from birth to 13 years. Only twenty-four of these were studied with the roentgen ray. No definite measurements were given, but he found no children with the hook formed stomach, up to the age of 3 years. He concluded that the visceroptotic habitus is found in children of the frail type, and that prolapse of the liver, kidney, stomach, and colon is seen only in rare instances in children under 12 years of age.

Butler, in 1910, reported observations on a series of 155 children, fifty girls and 105 boys. His conclusions were that evidences of enteroptosis are observable throughout childhood, but more often at puberty. In the first days after birth palpable liver and kidneys are common. Beyond the first year up to later childhood, palpable livers and displaced

1. De Buys, L. R., and Henrique, Adolph: Effect of Body Posture on the Position and Emptying Time of the Stomach, Am. J. Dis. Child. **15**:190 (March) 1918. Sever, James Warren: The Position of the Stomach in Children, Arch. Pediat. **31**:38, 1914

2. Petri: X-Ray Observations on the Lower Colon, Jahrb. f. Kinderh. **82**: 87, 122.

3. Smith, Richard R.: A Study of Children with Reference to Enteroptosis, J. A. M. A. **58**:385 (Feb. 10) 1912.

stomachs are exceptional, although signs of the habitus are evident in some of the children. The active ptoses he believes are seen at the period of puberty. No measurements are given, and roentgen-ray study was only partial.

Sever, in 1914, reported a series of examinations in eighty-three children, twenty-three of which were boys. The ages varied from 4 to 18 years. The children were normal in height, weight and nutrition, according to Holt's figures. He concluded that general condition and body weight had little to do with the position of the stomach. He also found the index of Bisher and Lenhoff, which is determined by dividing the jugulo pubic distance by the waist measure taken just below the ribs and multiplying by 100, gave little indication of the position of the viscera. He noted that of the eighty-three children, two showed the lower pole opposite the fourth lumbar vertebrae, and nine showed it at the level of the crests; and that in forty-nine the lower pole was well below the crests, sometimes as much as 3 and 4 inches (7.6 and 10.1 cm.). No exact measurements are given, except of extreme types.

He found that the shape of the stomach varied considerably, although the most persistent form was of the sink drain type. There were few steer horn shaped stomachs. None of these were seen in the position regarded as normal for the adult. Many were seen in the midline, but many were to the left, apparently resting well within the iliac fossae. He found only one pathologic case—that of a child with a dilated colon and constipation.

At the Lymanhurst school opportunity was offered for the study of a group of children whose ages varied from 6 to 7 years. Two hundred and fifty children were examined in a routine manner as follows: The children were given in the morning on an empty stomach one glass of water and one slice of bread.[1] Approximately forty-five minutes later the meal was aspirated and studied. They were then given about 300 c.c. of cereal and 2 ounces of barium sulphate and at intervals varying from three and a half to six hours later they were examined with the fluoroscope from the standpoint of motility. They were then given approximately 450 c.c. of buttermilk and 2 ounces of barium sulphate, their stomachs studied as to form, and plates were taken both lying and standing, the tube parallel to the umbilicus and 39 inches (99 cm.) from the plate.

The data obtained on the following points will be considered in this paper:

1. A brief record of the results of the Ewald meal.

2. The position of the stomach related to a line drawn at the level of the iliac crests.

3. The measurements of the intercostal angle and its relationship to the position of the stomach.

4. The palpability of the liver, kidneys and spleen and the motility of the stomach.

5. A report of two cases of dilated colon and constipation found in the series.

In a study of the children in this group from the standpoint of height, weight and general nutrition, Dr. Richard Scammon found that they compared favorably with an unselected group, according to the general standards used.

The results from the Ewald meal varied from a few cubic centimeters to 125 c.c. in amount, there apparently being no uniformity. Considerable variation in the actual time of taking the meal and tech-

TABLE 1.—*Free Hydrochloric Acid*

Age Period	No. Cases	Maximum Acid, Percentage	Minimum Acid, Percentage	Males, Average	Females, Average	Both Males and Females
6-17	230	58	0	20-30	20-30	20-30

TABLE 2.—*Total Acidity*

Age Period	No. Cases	Maximum Acid, Percentage	Minimum Acid, Percentage	Males, Average	Females, Average	Both Males and Females
6-17	230	80	7	40-50	40-50	40-50

nical difficulty in completely evacuating the stomach, particularly in patients of this age, undoubtedly are factors in this variation.

Figures 1 and 2 are self explanatory and show the range of free hydrochloric acid and total acidity. The findings portrayed in these illustrations are given in Tables 1 and 2. In the series of 230 cases in which this was plotted, the free hydrochloric acid ranging from 0 in four cases to 55 in one, the average being 40-50. The curves of free and total acidity follow each other up and down in marked uniformity.

In the four cases with no free hydrochloric acid, only two could be subsequently examined. Of the two examined about one year later, one showed a free hydrochloric acid of 18. The other still showed complete absence of free hydrochloric acid.

In the study of the position of the stomach, a line drawn between the iliac crests was used as the zero point. At first I tried to use a marker at the umbilicus, but I found it inaccurate. Roughly, however, in these observations the level of the umbilicus was found to correspond well with the iliac crests in the standing position.

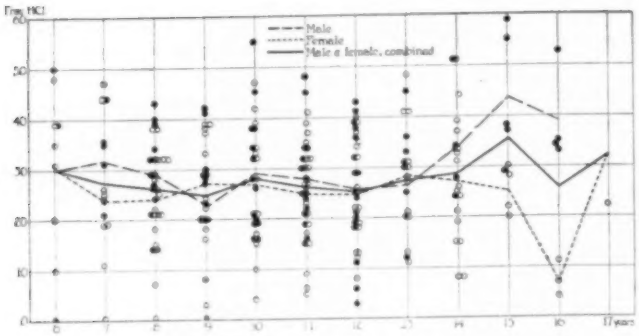

Fig. 1.—Free hydrochloric findings. The figures running vertically represent the free hydrochloric acid. The figures below represent age periods of the children.

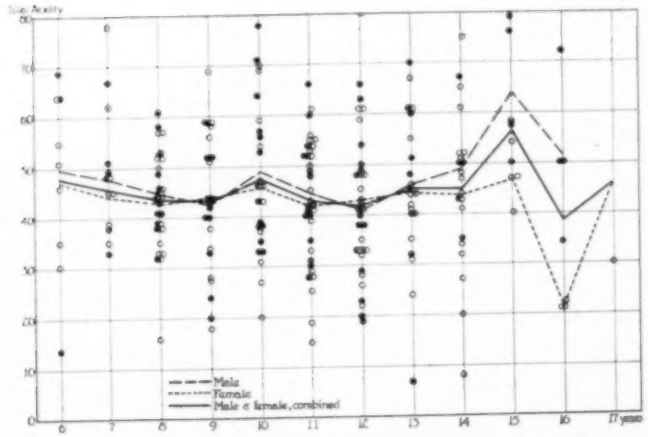

Fig. 2.—Total acidity findings. The figures running vertically represent the total acidity. The figures below represent age periods of the children.

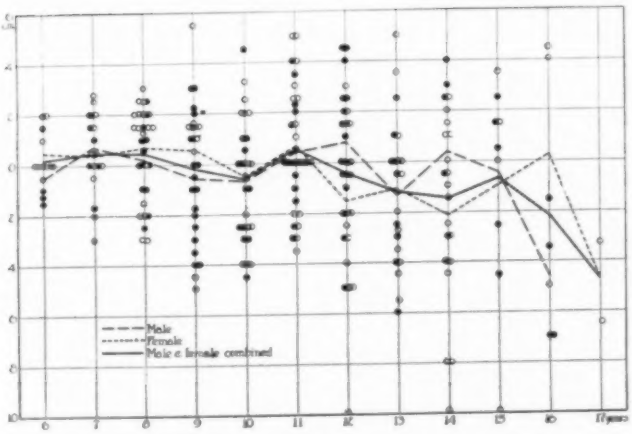

Fig. 3.—Position of the lower pole of the stomach, zero being taken as the line drawn to the iliac crests and the figures on the right being above and below the crests (in centimeters). The figures below are the ages of the children in years. In this summary, the children aged 16 and 17 were not counted because there were so few of them.

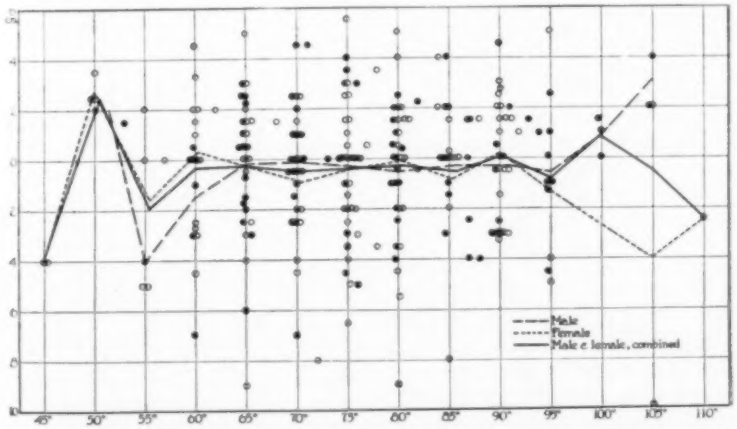

Fig. 4.—Relationship between the position of the lower pole of the stomach and the intercostal angle. The figures on the right represent the distance above and below the line drawn from the iliac crests which is taken as zero, and the intercostal angle in degrees.

Figure 3 shows the position of the stomach (also shown in Table 3), O being the crests and the distance above and below in centimeters, for the various ages from 6 to 17 years inclusive, the highest being nearly 6 cm. above the crests, the lowest 10 cm. below the crests, of which there were three. The average lies close to the iliac crests with a slight tendency downward, after the age of 11. Yet, it is an exceedingly uniform variation in both directions. From this chart, although there are some very low stomachs, it would be difficult to determine where the position becomes pathologic. One might call the group below 6 cm. pathologic, as they seem to stand more in a class by themselves. These are all over 13 years. However, is it much more extreme relatively at this age than a stomach 5 cm. below at the age of 9 or 3 cm. below at the age of 7?

TABLE 3.—*Position of Stomach with Distance from Iliac Crests to Lower Pole*

	Male		Female		Both	
Age	Average Distance, Cm	Number of Cases	Average Distance, Cm.	Number of Cases	Average Distance, Cm.	Number of Cases
6 to 15, inclusive	—0.54	105	—0.38	130	—0.27	235
6 to 11, inclusive	—0.11	70	—0.33	82	+0.22	152
12 to 15, inclusive	—0.21	35	—1.47	48	—0.84	83

TABLE 4.—*Iliac Crest to Lower Pole of Stomach with Intercostal Angle*

Both Male and Female			Male			Female		
Average Angle	Average Distance to Lower Pole	No. Cases	Average Angle	Average Distance to Lower Pole	No. Cases	Average Angle	Average Distance to Lower Pole	No. Cases
77.7	—0.49	243	77.8	—0.18	109	76.0	—0.89	134

In the total series, 101 cases were above the iliac crests, or 42 per cent.; 103 cases, or 42 per cent., were below the crests, and thirty-nine cases, or 16 per cent., were at the iliac crests.

In measuring the intercostal angles, I marked the costal margins with a pencil and then transferred it to tracing paper and measured the angle. The intercostal angle is often used clinically as an indication of the position of the abdominal viscera. In Figure 4 the relationship between the position of the lower pole of the stomach measured from the iliac crests and the width of the intercostal angle is shown (Table 4). The intercostal angle was seen to vary from 45 to 110 degrees. The average position of the stomach seemed to bear no relationship to the intercostal angle, as one might expect. However, no high stomachs were found in cases with narrow costal angles, and no low stomachs in the cases with extremely wide angles. But, in the cases between 55 and 95 degrees, there appears to be no definite relationship. For instance, at the angle of 65 degrees we have cases varying from 5 cm. above to

9 cm. below; at 80 degrees, from 5 cm. above to 9 cm. below, and at 55 degrees, from 2 cm. above to 5 cm. below. This seemed to be equally true of males and females, the curves running quite uniformly for both sexes.

In order to show graphically the position of the stomach at the various age periods, outlines of the stomach were superimposed. The outlines first being marked on the roentgen-ray plate and transferred to a sketch of the pelvic and lumbar skeleton, the two fixed points used being the vertebral column and a line drawn between the iliac crests.

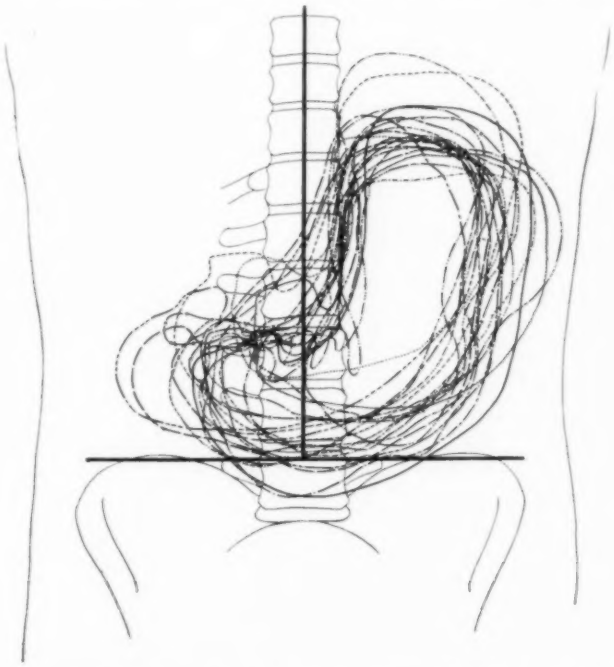

Fig. 5.—The outlines of the stomachs of twenty children at the ages of 6 and 7, superimposed. The fixed lines are the middle of the vertebral column and the crests of the ilium, showing the stomach somewhat farther to the right than in later childhood, and much less variation in the position of the stomach. The general shape of the stomach varies from the sink drain to the very blunt hook.

Twenty cases were used in each sketch and the age periods 6 and 7 were grouped because there were not cases enough to make twenty of either age group, then 8, 10, 12 and 14. With each composite group is a sketch showing the four most common variations.

As the age increases there is apparently a much greater variation in outlines and also in position, both in relation to the two fixed lines—

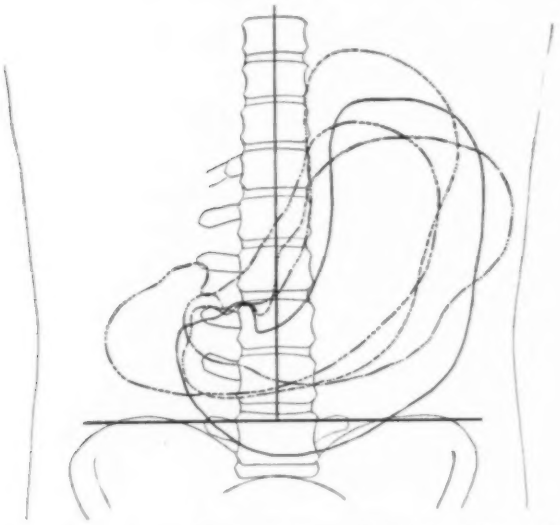

Fig. 6.—The four extreme outlines selected from Figure 5.

Fig. 7.—A composite group made the same as in Figure 5, showing more variation in the position of the stomach at the age of 8, an appreciable tendency to the hook form and more variation in the type.

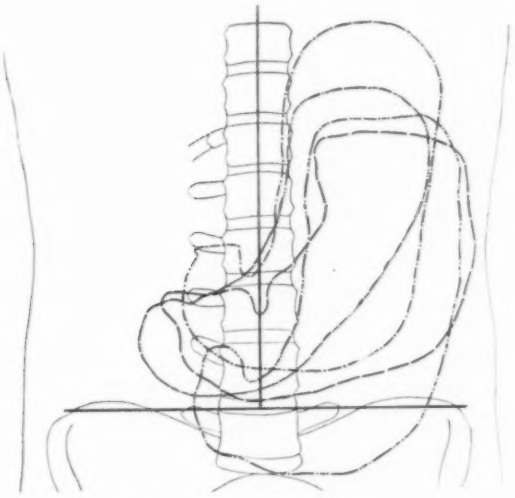

Fig. 8.—The four extremes of Figure 7.

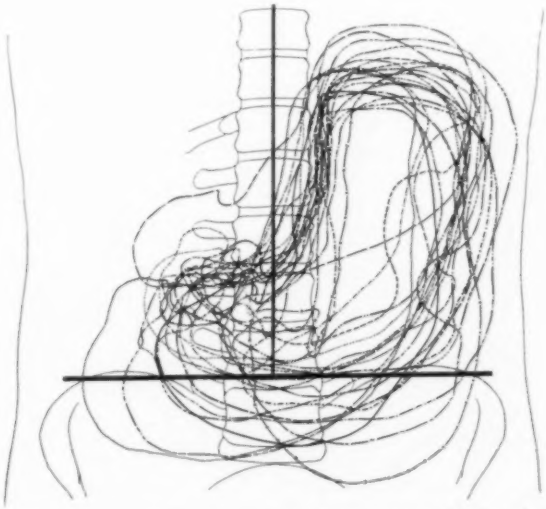

Fig. 9.—The outlines from a group of 10 year old children, showing more variation in type than in the previous ages. The stomach as a whole apparently comes more to the left and generally is more nearly the hook type.

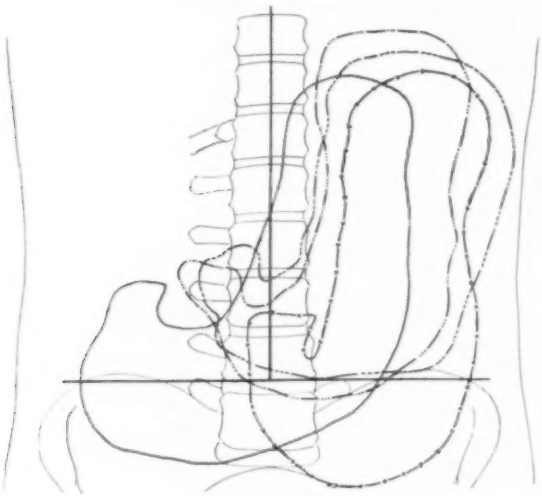

Fig. 10.—The four extremes of Figure 9.

Fig. 11.—A group of 12 year old children, showing a general tendency to lower stomach, and more definite hook form and still wider variation in the outlines of the stomach.

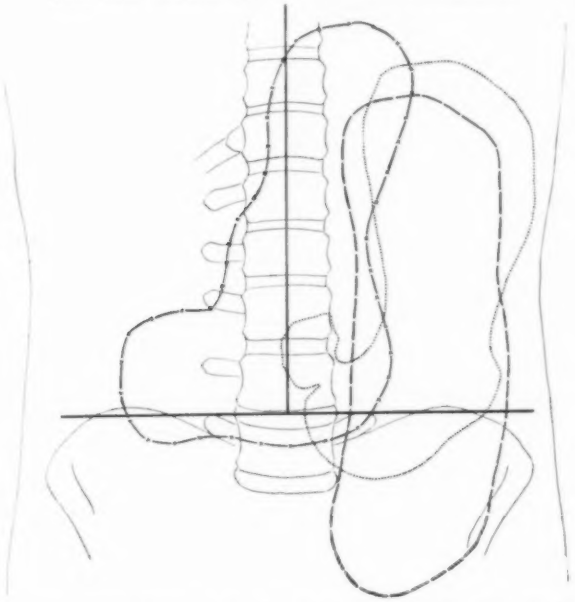

Fig. 12.—The three extremes of Figure 11. The one farthest to the right is the highest.

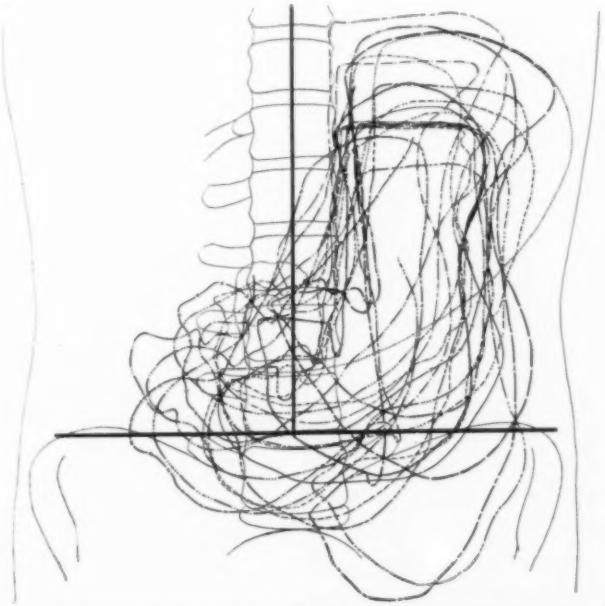

Fig. 13.—A group of 14 year old children, showing still more variation in form, lower stomachs and rather unformed hook shape.

the iliac crests—and the vertebral column. In the 6 and 7 year group there seems to be a closer approximation of outlines with more tendency to the sink drain stomach than at older periods, the sharp hook definitely becoming the characteristic type at the age of 12.

In 243 cases, the liver, kidneys or spleen were palpable in thirty-three cases. The ages in this group of thirty-three varied from 6 to 15 years, and the number at each age period was as follows: age 6, one case; age 7, three cases; age 8, five cases; age 9, two cases; age 10, four cases; age 11, three cases; age 12, five cases; age 13, five cases; age 14, one case, and age 15, three cases, showing a general distribution among the various ages. In these thirty-three cases, the stomach was below the iliac crests in fifteen, or 47 per cent. In the whole group of 243 cases, in 101, or 42 per cent., the stomach was below the crests, showing too slight a relationship between the palpability of these organs and low stomach to be of any clinical significance. The average costal angles in the thirty-three cases was 72 degrees; the average costal angle for the whole series was 76 degrees. This again shows a slight relationship between the narrow costal angle and the palpability of the liver, spleen and kidneys in this group.

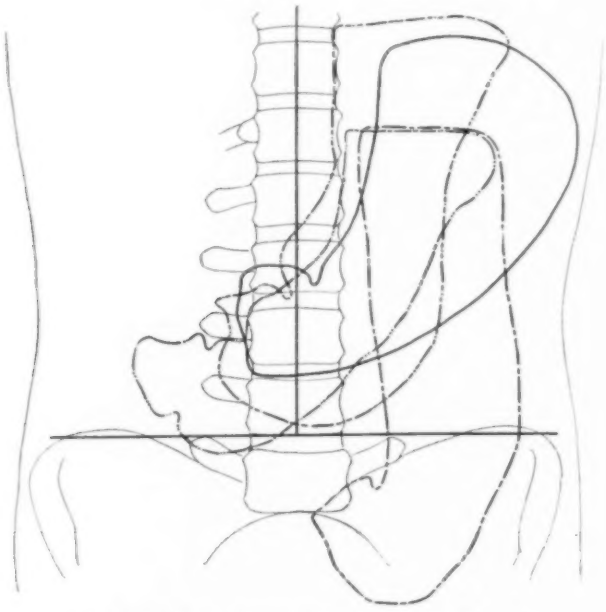

Fig. 14.—Four extremes taken from Figure 13.

In twenty-three cases, the liver was palpable. In four cases, the spleen was palpable. In eleven cases, the right kidney was palpable. In three cases, both the liver and kidney were palpated. In none of the cases were the liver, right kidney and spleen all palpable in the same case. The left kidney was palpated in none of the cases. There were seventeen females and sixteen males in the series with right kidney, liver or spleen palpable. The right kidney was palpable in eight females and three males. The spleen was palpable in one female and five males. The liver was palpable in eight females and fourteen males.

In this series, there were two cases of dilated colon associated with constipation—one that of a girl aged 13, the other a boy aged 9, both unrecognized before; both gave a history of constipation dating from birth with attacks of more marked constipation requiring enemas and purgatives.

SUMMARY

In children from 6 years to 15 years, the free hydrochloric acid and total acidity is apparently the same as in adults. Absence of free hydrochloric acid was found in four cases of the 250. In two of these cases examined one year later, one showed no free hydrochloric acid, and the other showed a small amount of acidity.

The position, size and shape of the stomach varies widely at all ages from 6 to 15, showing a great variation as puberty is approached. The sink drain type of stomach is more common in younger children, the sharp hook in older children. In 42 per cent. the stomach was above the crests of the ilium, in 42 per cent. below the crests and in 16 per cent. at the crests.

There was little relationship if any between the intercostal angle and the position of the stomach. This also holds true for the position of the liver, right kidney and spleen. Palpable liver and right kidney is common in children of all ages.

In this group of cases, there was found no difference in the gastric chemistry, motility or costal angles between males and females. The position of the stomach was the same up to the age of 11, when there was an appreciable tendency to lower stomachs in females than males. In regard to the palpability of the abdominal viscera, there was practically an equal distribution of palpable abdominal organs between the sexes, seventeen females and sixteen males. The right kidney was felt much more frequently in females, the liver and spleen more frequently in males. Two cases of dilated colon were found which had previously been unrecognized; both in cases having constipation from birth. Sever found one in eighty-three cases, indicating that dilated colon is found in approximately 1 per cent. of children. Undoubtedly

all cases of constipation dating from birth should be carefully studied with this condition in view. The motility of the stomach and intestines is greater in children than in adults. This seems to be especially true of the colon.

CONDUCTION CHANGES ACCOMPANYING PERICARDIAL EFFUSION

WITH A CONSIDERATION OF A LOCAL CIRCULATORY FACTOR IN HEART BLOCK *

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NEW YORK

To the effect of pericardial effusion on heart function scant attention has been paid by pathologic physiologists; while clinical emphasis has been directed toward those external manifestations—chiefly the manner and degree of the extension of the limits of cardiac dulness—which provide essential means for the diagnosis of accumulation of liquid in the pericardial cavity. Moreover, the picture is so frequently complicated by a concomitant infection and by inflammatory lesions in the heart muscle or valves that the intrinsic effect of the effusion is obscured. Thus MacKenzie [1] dismisses the subject by stating that he has "never found any very serious embarrassment of the heart from extensive pericardial effusion, the reason being probably that while the normal pericardium is a more or less inelastic bag, with the inflammatory invasion it becomes distensible, and therefore able to accommodate an enormous amount of fluid with little embarrassment to the heart."

On the other hand, Calvert,[2] in 1907, found marked compression of the heart and its vessels in two cases of large effusion into the pericardium, and on the basis of these anatomic findings discussed the circulatory changes that might be expected under the conditions of altered pressure. Thomas Lewis,[3] in 1910, from studies on cats, concluded that "the heart is peculiarly susceptible to the changes of pressure external to it," finding that a rise in intrapericardial pressure of 1 mm. of mercury lowered systemic pressure on an average of from 8 to 9 mm. of mercury. More recently, Kuno [4] has studied in dogs the mechanical effect of liquid in the pericardium on the functions of the heart, and he found that circulation ceased when intrapericardial pressure equaled venous pressure, a confirmation of Calvert's deductions. As might be expected, small increases in intrapericardial pressure brought corresponding decrease in cardiac output and arterial tension, up to a certain threshold, beyond which a distinct fall occurred.

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* From the Cardiac Clinic of the New York Hospital.

1. MacKenzie, Sir James: Disease of the Heart, Ed. 3, London, 1918, p. 283.
2. Calvert, W. J.: Bull. Johns Hopkins Hosp. **18**:403 (Oct.) 1907.
3. Lewis, Sir Thomas: J. Physiol. **37**:213 (Aug. 12) 1908.
4. Kuno, Y.: J. Physiol. **51**:221 (Sept. 12) 1917.

To these scattered observations of pericardial pressure effects, we wish to add the clinical record of a man with a large pericardial effusion, accompanied by a well marked depression of conductivity of the bundle of His, which was readily converted by vagus pressure into 2:1 auriculoventricular block. These phenomena disappeared at once after the tapping of 500 c.c. of pericardial liquid. A further point of interest was a definite hypertension, which fell steadily until normal limits were reached and maintained.

REPORT OF A CASE

History.—J. R., a man, aged 57, was admitted Feb. 23, 1921, to the New York Hospital, in the service of Dr. Lewis A. Conner. The chief complaint was shortness of breath and heaviness in the abdomen. The family history was irrelevant, and the patient recalled no childhood or adult infections. His health had been excellent until five months before admission when he awoke in the middle of the night with difficulty in breathing. With remissions from time to time, this dyspnea continued to progress; it was always relieved when the patient assumed an upright position.

Physical Examination.—This disclosed an orthopeic, sparely nourished elderly man, with moderate pallor, puffiness under the eyes, and edema of the hands, scrotum and lower part of the legs. The pupillary reactions were normal, the knee jerks active. The jugular veins were not distended. The chest was emphysematous; at both bases, tactile fremitus was diminished, with dulness and diminished breathing. The apex impulse was not seen; it was felt diffusely in the third, fourth and fifth interspaces in the region of the left nipple. Relative cardiac dulness extended in the first interspace 5.5 cm. to the right and 4 cm. to the left of the midsternal line, and the greatest transverse measurements was 10.5 cm. to the right in the fifth interspace and 15.5 cm. to the left in the sixth interspace. The outline was typically pyriform. The sounds were faint; there were no murmurs. The rhythm was regular, the rate 80 per minute, at the apex and wrist. Blood pressure was: systolic 190, diastolic 120, with no evidence of alternation. On pressure on the right vagus, there was a slowing of ventricular and radial rates to from 42 to 44 beats a minute. There was a transitional period of irregular rhythm following vagus stimulation. The liver edge was 6 cm. below the right costal margin; there was shifting dulness in the flanks. The fundi showed moderate sclerosis of the retinal arteries, in keeping with a definite though not marked peripheral sclerosis. There was no retinitis.

Laboratory Findings.—These were: hemoglobin, 70 per cent.; white blood cells, 9,800; polymorphonuclear leukocytes, 80 per cent.; Wassermann reaction, negative; urine, of high concentration, with a cloud of albumin, numerous granular casts, and white blood cells.

Electrocardiograms.—These were taken on admission prior to the administration of digitalis. They showed normal sinus rhythm at a rate of 80 per minute, with prolongation of the auriculoventricular conduction time in Leads I and III to 0.44 second. In Lead II the rate was slower, 74 per minute, and the *P-R* interval equaled 0.22 second. The ventricular complexes showed a slight right predominance, and were remarkable for the small size of the waves, which indicated a poor functional state of the heart muscle, as did the flat T-waves. The second record, taken during pressure on the right vagus, showed a transitory period of 2:1 heart block, followed by varying grades of auriculoventricular dissociation. In Lead III, there were *P-R* intervals of 0.6 to 0.68 of a second.

Course.—On February 24, three days after admission, because of failure to improve under rest and digitalis, 500 c.c. of pericardial liquid was withdrawn through a needle inserted close to the sternal border in the fifth left interspace.

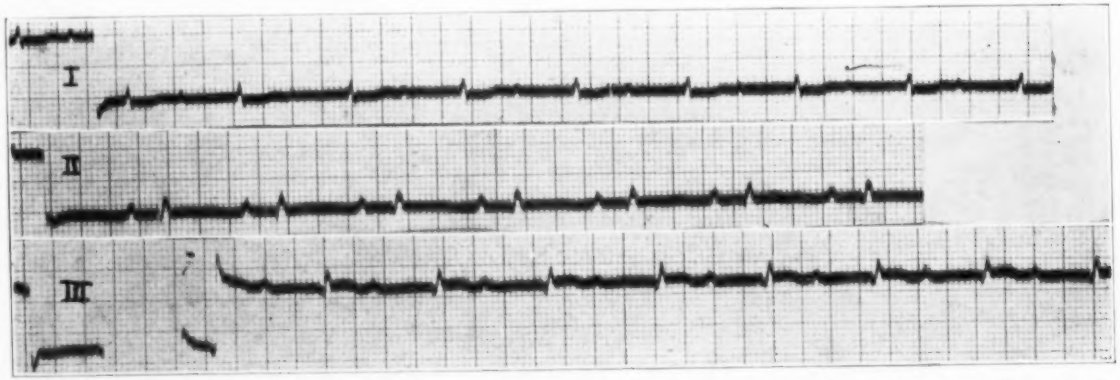

Fig. 1.—E. K. G., Feb. 21, 1921: *P-R* interval 0.44 second in Leads I and III; 0.22 second in Lead II, amplitude of *QRS* group greatly diminished; T-waves flat.

The tapping gave the patient immediate and great relief. The pericardial fluid had a specific gravity of 1.024, 12 gm. of albumin per liter, and 6,690 white blood cells, 96 per cent. lymphocytes, per cubic millimeter. Cultures and guinea-pig inoculation were sterile. On the day after paracentesis, a third electrocardiogram revealed a normal conduction time of 0.15 second, and a slight but definite increase in amplitude of the *QRS* group, as evidence of improved myocardial function.

After an uneventful convalescence, the patient was discharged on March 13, but three weeks later the heaviness in the abdomen and dyspnea returned, and the patient came back for a second tapping of 500 c.c. on May 5. On this occasion, the fluid contained 2,400 cells per cubic millimeter, almost entirely lymphocytes. Renal function tests at this time were within normal limits: urea nitrogen 9.2 mg., plasma chlorids 625 mg., and the phenolsulphonephthalein output 52 per cent. in two hours. The specific gravity in two hourly urine specimens varied from 1.026 to 1.030. The electrocardiograms showed no change in conduction time during this readmission.

In December, 1921, after six months of freedom from symptoms, the oppression and the signs of effusion returned, and the patient was sent in from the cardiac clinic for a third paracentesis, which yielded 550 c.c. On this occasion also the electrocardiogram recorded normal conduction time.

In the twenty months since the last tapping, there has been no evidence of return of fluid, and it is noteworthy that the series of electrocardiographic records shows a gradual increase in the size of the *QRS* group and a slight rise in the T-wave. On the whole, there has been a coincident improvement in the man's general condition and cardiac response.

ETIOLOGY OF HEART BLOCK

Reference to an authoritative text [5] discloses that auriculoventricular heart block may be divided into three groups, according to the factors that give rise to the depression or failure of conduction over the bundle of His: (1) alterations in structure of the junctional tissues; (2) intoxications involving the bundle or its branches; (3) nervous influences, chiefly through the vagi, exerted on the conduction system.

The first group undoubtedly comprises by far the greatest number of cases of block, particularly the numerous examples of inflammatory and degenerative lesions incident to acute rheumatic [6] and other infections. Gumma of the bundle is another well recognized cause of heart block.[7] The instances of sclerosis of the junctional tissues are many, but here, it must be admitted, there is much lack of distinctness regarding both histology and functional pathology. We have in mind, as an example, a person with classical complete block and convulsive attacks, in whom the anatomic findings were minimal in respect to fibrosis or other changes in the junctional tissues. A series of similar instances of clear-cut clinical pictures without demonstrable anatomic bases has been

5. Cohn, A. E.: Cardiac Irregularities, Nelson Loose-leaf Medicine, New York **4**:333E, 1920.

6. Christian, H. A.: Med. & Surg. **1**:911, 1918.

7. Major, R. H.: Stokes-Adams' Disease Due to Gumma of the Heart, Arch. Int. Med. **31**:857 (June) 1923.

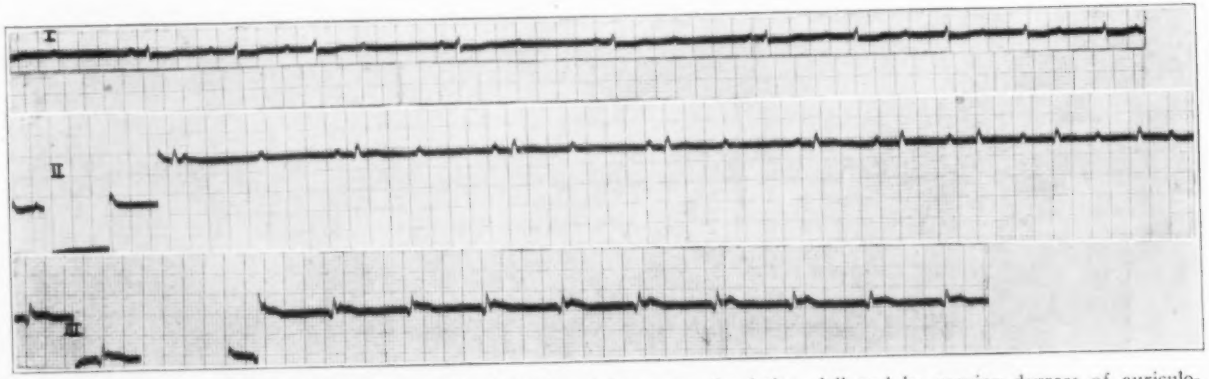

Fig. 2.—E. K. G., Feb. 21, 1921: 2:1 heart block during right vagus stimulation, followed by varying degrees of auriculo-ventricular dissociation. In Lead III, *P-R* interval equals 0.68 second.

reported. Such observations, in the opinion of Krumbhaar,[8] "tend to show that heart block, even when complete, may not only be temporary, but may depend on a much more complex condition than a simple lesion or destruction of the bundle of His."

Digitalis, of course, provides the greater number of cases in the second group, while a number of less commonly used drugs, diphtheria toxin and the products of intestinal toxemia and of asphyxia have been found involved in specific instances.

While various lesions along the course of the vagi, of which tumors of, or encroaching on, the vagal ganglions and diabetic neuritis involving the trunks are outstanding examples, have been reported as definite etiologic factors in heart block, it remains commonly true that it is unusual for vagal effect to be other than a relative bradycardia, except in hearts that are already damaged. This point of view is corroborated by the recent careful work of Kleemann.[9]

In this generally accepted etiologic classification of heart block which we have briefly reviewed, the case that we report is not easily included. Except for the remote possibility of tuberculosis, infectious factors appear to be eliminated; the impairment of conduction preceded administration of digitalis and was absent at the height of digitalis effect; after the first paracentesis, vagus stimulation was no longer effective, while the hypothesis of pressure on the nerve trunk by a distended pericardium or its contents, in a manner analogous to recurrent laryngeal nerve compression by auricular enlargement, dilatation or upward displacement of the pulmonary artery or aneurysm, seems beyond the bounds of anatomic possibility. What, then, was the cause of the lowered conductivity of the junctional system and the abnormal vagal effect accompanying this pericardial effusion?

The answer to this question, we believe, is to be found in the impaired blood supply to the bundle of His as a result of the direct interference with the intrinsic cardiac circulation by the pressure of the effusion on the coronary arteries and veins. To the decreased arterial in-flow and the increased venous congestion thus arising, must be added the embarrassment of coronary circulation due to the changes in intracardiac pressure relations which result from compression of the auricles.

Besides the deductions of Calvert already mentioned, drawn from pathologic evidence of compression, there is accumulating clinical data that have an important bearing on the point at issue of a circulatory

8. Krumbhaar, E. B.: Adams-Stokes' Syndrome, with Complete Heart-Block, Without Destruction of the Bundle of His, Arch. Int. Med. **5**:583, (June) 1910.

9. Kleemann, M.: Deutsch. Arch. f. klin. Med. **130**:221 (Sept. 26) 1919.

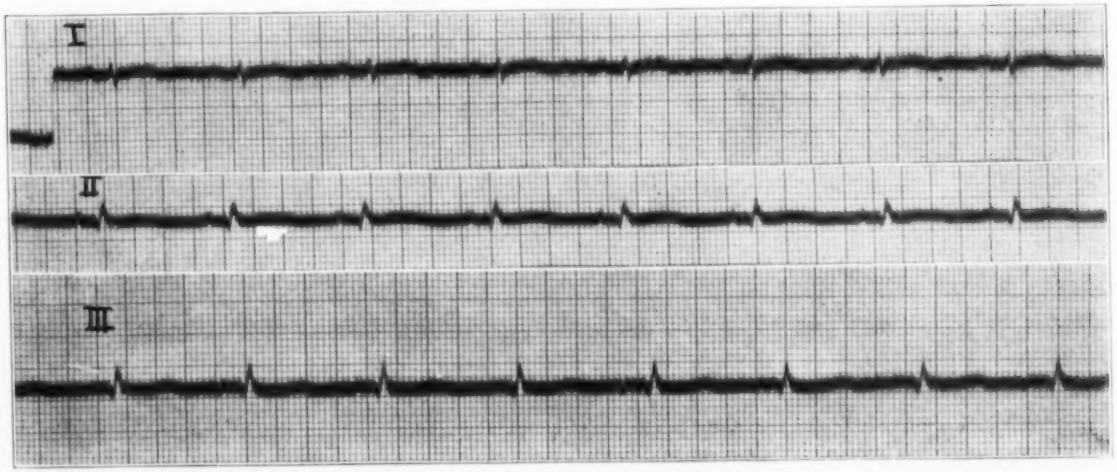

Fig. 3.—E. K. G., Feb. 28, 1921: Following removal of 500 c.c. of pericardial liquid, *P-R* interval 0.15 second.

factor in heart block. Pardee [10] has called attention to the occurrence of block of varying degree, usually only of delay in conduction, in patients with cardiac decompensation, and I have recently had an instance in the case of a woman aged 50, who came under observation complaining of shortness of breath on moderate exertion. The electrocardiogram showed a *P-R* interval of 0.22 second, a delay in conduction which has disappeared with restoration of cardiac sufficiency by rest. Herrick [11] has also commented on the disappearance of heart block under the improved circulatory conditions brought about by digitalis therapy. Twenty years ago, Wenckebach [12] wrote that the power of conduction was dependent in the first place on the presence of oxygen, and Hirschfelder [13] has suggested that ischemia may be sufficient to diminish conductivity.

A rather striking example of this circulatory factor in heart block is a case of complete dissociation accompanying auricular fibrillation recently reported by Neuhof,[14] in which there was the anatomic finding of complete calcification of that small branch of the coronary artery that supplied the auriculoventricular node. Although the sclerotic changes had been of many years' duration, and degeneration along the course of the auriculoventricular artery was present, the history and clinical evidence pointed to a sudden onset of the block, presumably due to final complete closure of this small vessel. Of doubtful import is Gerhardt's [15] example of sclerosis of the artery supplying the *A-V* bundle, since cellular infiltration in the course of rheumatic fever was also present.

With such facts in mind, it seems not improbable that a certain number of cases of heart block, particularly among those of a functional [16] or transient type, may fall into a circulatory group, with diminution or failure of the blood supply to the junctional tissues as the immediate etiologic factor. Such an ischemia or anemia of the conduction system would serve to explain certain of the clinical and electrocardiographic phenomena of block, as well as the paucity of anatomic findings in instances of definite clinical disease. For example, some

10. Pardee, H. E. B.: The Relation of Heart-Block to Lesions of the Auriculoventricular Bundle, with Report of a Case, Arch. Int. Med. **11**:641 (June) 1913.

11. Herrick, W. W.: Am. J. M. Sc. **139**:246 (Feb.) 1910.

12. Wenckebach, K. F.: Arrhythmia of the Heart, trans., Snowball, Edinburgh and London, 1904.

13. Hirschfelder, A. D.: Diseases of the Heart and Aorta, Ed. 3, Philadelphia, J. B. Lippincott Co., 1918, p. 579.

14. Neuhof, S.: Am. J. M. Sc. **165**:34 (Jan.) 1923.

15. Gerhardt, D.: Deutsch. Arch. f. klin. Med. **103**:485 (July 30) 1908.

16. Hart, T. S.: Am. J. M. Sc. **149**:62 (Jan.) 1915.

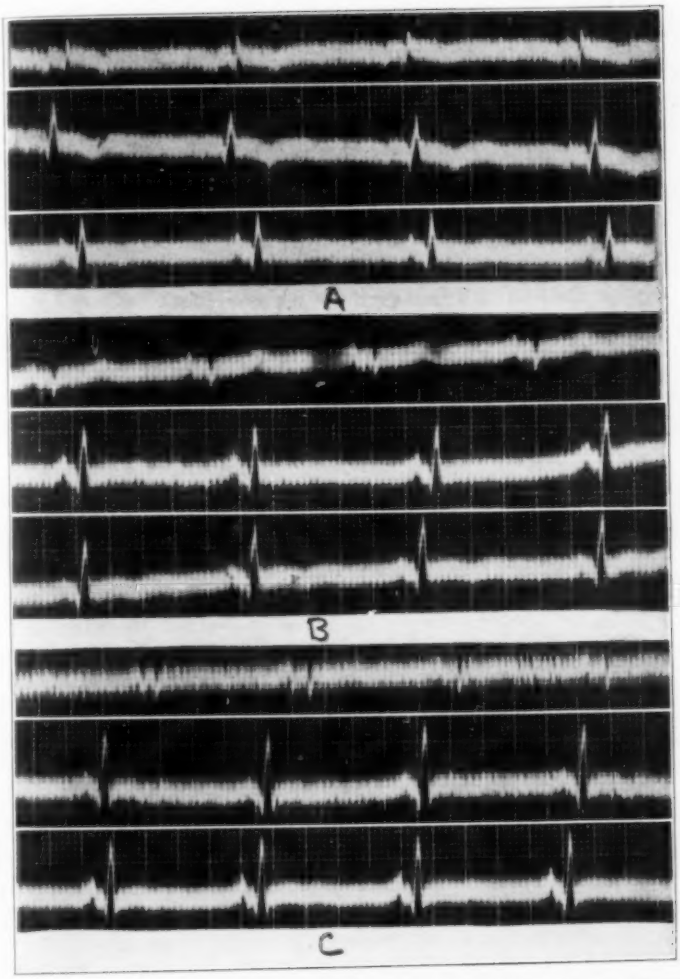

Fig. 4.—(*A*) E. K. G., Dec. 6, 1921; (*B*) Aug. 17, 1922; (*C*) Nov. 15, 1922: These records show increasing amplitude of the *QRS* group coincident with the patient's general progress; normal conduction time in all.

of the instances of block associated with hypertension [17] might readily fall within this clinical group. It would appear that attention directed toward the circulatory factor in heart block might aid in clearing up some of the present obscurity of its functional pathology. The necessary anatomic groundwork has recently been reviewed and added to by Gross.[18]

SUMMARY

The occurrence of auriculoventricular heart block accompanying a large pericardial effusion is reported, with disappearance of the block following tapping.

The compressive effect of pericardial effusion on the heart is discussed, with particular reference to the embarrassment of intrinsic circulation through pressure on the coronary arteries and veins.

Impairment or failure of blood supply to the conduction system is pointed out as a possible cause of certain instances of heart block, especially those of transient or functional nature.

When the effects of infection, poisoning or nervous influences may be eliminated, the reasonableness of considering a local circulatory factor as a cause of block is suggested.

17. Musser, J. H., Jr.: Heart Block Associated with High Blood Pressure, Arch. Int. Med. **20**:127 (July) 1917.

18. Gross, L.: The Blood Supply to the Heart in Its Anatomical and Clinical Aspects, New York, Paul B. Hoeber, 1921.

SYMPTOMATIC POLYCYTHEMIA WITH CYANOSIS AND DYSPNEA*

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DETROIT

The purpose of this paper is to call attention to a group of cases showing the clinical signs of Ayerza's disease (sclerosis of the pulmonary artery) due to another pathologic condition and to offer some points which will aid in differentiating the various pathologic processes which may cause this syndrome.

Parkes Weber [1] classifies the pathologic conditions associated with "secondary" (symptomatic) forms of polycythemia rubra, and mentions the following classes of cases:

1. Polycythemia hypertonica, "Geisböcks disease."

2. Splenomegalic polycythemia rubra associated with tuberculosis of the spleen.

3. Secondary polycythemia rubra with splenomegaly connected with a condition of visceral blood stasis of chronic thrombotic origin in the portal and splenic veins.

4. "Cardiacos negros," "Ayerza's diseases," due to pulmonary sclerosis, pulmonary fibrosis, asthma, pulmonary emphysema, chronic bronchitis and pleural adhesions.

5. Secondary polycythemia rubra connected with congenital or acquired heart disease.

It will be seen that under Ayerza's disease, Parkes Weber groups all cases of erythrocytosis of pulmonary origin whether the pathologic process is primary in the pulmonary artery or elsewhere in the pulmonary or pleural tissues.

There is a distinct group of cases presenting the picture of extreme cyanosis, especially of the upper parts of the body, with marked injection of the conjunctivae, attacks of dyspnea of an asthmatic character, and profuse mucopurulent and bloody expectoration coupled with gradually developing erythremia. When we examine these cases for the common etiologic factors concerned with cyanosis and dyspnea, we find that the usual mechanical factors accompanying such a condition are lacking.

Valvular disease of the heart, collections of fluid in the serous cavities and mediastinal tumor are ruled out in turn. No outstanding physical signs are elicited to account for the patient's condition. The

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1. Weber, F. Parkes: British M. J. **2**:658 (Oct. 30) 1920.

history is usually as follows: A middle aged man gradually develops a cough with mucopurulent expectoration. The patient later notices that he becomes breathless on exertion and still later that definite attacks of dyspnea somewhat asthmatic in character become increasingly frequent, and cyanosis is gradually noticed developing as the attacks of dyspnea become more severe. The cyanosis gradually deepens and becomes especially prominent during the asthmatic attacks, but is still markedly noticeable in the interim. At this stage the patient usually seeks medical aid, and a physical examination is usually made during an attack while the patient is propped up in bed and is extremely dyspneic. The dyspnea is not the typical expiratory dyspnea of spasmodic asthma, but inspiration and expiration are equally labored, coupled with profuse mucopurulent sputum. The face is livid; the lips and ears are often almost black, and the conjunctivae are a deep red in sharp contrast to the blue lividity of the rest of the face. The patient appears extremely anxious, and the accessory respiratory muscles are all called into play. The chest is usually barrel shaped and emphysematous in type. The intercostal spaces show little retraction during inspiration, and the abdominal movements are of the normal type. Cyanosis of the lower extremities may be marked during attacks but is usually less marked than that of the head and neck. In cases uncomplicated by myocardial exhaustion, there is no edema of the feet and extremities, and no fluid can be detected in the abdomen. The apex beat may or may not be seen, and when noted is usually inside the nipple line and diffuse in character. On palpation no signs are elicited which give a clue to the condition of affairs. Tactile fremitus may be slightly decreased or definitely increased throughout. On palpation of the abdomen, the liver may sometimes be felt below the costal margin; occasionally the spleen is palpable, but more often not. An especial feature of the syndrome is the absence of striking splenic enlargement.

Percussion reveals a somewhat hyperresonant note such as is expected in emphysema. The area of cardiac dulness is not enlarged, and the right border of the heart is obscured by the hyperresonant anterior border of the right lung. In some cases an indefinite widening of the substernal dulness can be made out above the heart. Auscultation of the cardiac apex brings out a normal or practically normal first sound, and a normal relation between the first and second sound is noted at the base. During an asthmatic attack gallop-rhythm may be noted, and after a prolonged paroxysm an indefinite systolic murmur is often associated with the gallop-rhythm and heard throughout the paroxysm. In the intervals between the attacks of dyspnea, all cardiac signs are negative. The breath sounds are emphysematous in type with prolonged harsh expiration. Many râles of all types are heard during the asthmatic attacks, and the vibrations of coarse rhonchi may even be felt through

the chest wall. The sputum is copious, mucopurulent in character, richly blood streaked, or diffusely pink during the paroxysms, and may have special features such as anthracotic phagocytes. Curschmann's spirals, Charcot Leyden crystals, or eosiniphilia such as are found in true asthma are lacking.

The outstanding feature of the laboratory findings is the polycythemia of moderate grade. The red count is 7,500,000 or over, and usually not below 6,500,000. Hemoglobin estimations range from 100

Fig. 1.—Extreme pulmonary anthracosis with cavitation.

to 120 per cent. The leukocyte count is slightly elevated or normal, with a normal percentage relation of the various white cells. The urine has no special features.

It will be noted that thus far we have evidence of a severe disturbance of aeration of the blood, cyanosis, dyspnea and polycythemia, without the gross mechanical factors mentioned above to account for it. The difficulty must be sought in a disease of the external respiratory membranes themselves rather than in some gross mechanical factor—that is, in those tissues concerned in the interchange of gases between the outside air and the blood.

The pathology of one group of these cases was first recognized by Ayerza under the title "cardiacos negros" (Warthin [2]) and especially emphasized by Warthin [2] in America; by F. Parkes Weber [1] in England and by Bezancon [3] in France.

The following records are given to show that typical clinical signs of "cardiacos negros" or "Ayerza's disease" are not uncommonly found due to diffuse fibrosis and destruction of the pulmonary parenchyma from extreme anthracosis as in the case of coal miners or to chronic diffuse infection of unknown etiology.

REPORT OF CASES

CASE 1.—*History.*—A man, aged 40, complained of cyanosis and dyspnea. The patient was admitted to the hospital in a wheel chair and was put to bed. He was of Polish extraction. He rested propped up in bed. His respirations were 20, pulse 96, temperature 98.8 F. There was marked cyanosis involving the entire body but most marked about the lips and ears. His breathing was regular; there was no particular distress. He said that he had no pain. He was at once sent out on the fresh air pavilion. Oxygen was given, and the cyanosis cleared up within a few minutes. He was talking rationally and said that he would be all right after resting a little while.

The patient said that he had had a similar sickness about one year before and had quickly recovered. He had gone back to work and had been working steadily ever since. A friend said that he had been drinking a good deal of "moonshine" whisky. The friend said that the patient had frequently been "fighting" drunk. His wife said that the patient had had a cough for the past eight years and that he had been raising blood for the past two years. He had been employed all his life as a coal miner or worker in coal yards. He had had several attacks of cyanosis. He had been mildly delirious at home. On several different occasions his clothes had been set on fire. He had been taken to the hospital in January with a condition of marked cyanosis, from which he had recovered. A diagnosis of polycythemia had been made. The blood cells numbered 7,500,000.

Physical Examination.— The patient was resting in bed. There was marked cyanosis of the lips, ears and hands. There was a lesser cyanosis covering the entire body. He was perfectly conscious and talked freely. His head, eyes, ears and nose were negative. His teeth were in poor condition. There was marked pyorrhea. There was a small ulcer on the mucous membrane of the lower lip where it touched the sharp edge of a tooth. There was a thick yellowish secretion in the mouth. The throat was reddened. There was no rigidity of the neck. The chest was poorly nourished, symmetrical in shape. Intercostal spaces were prominent. Respiration was equal on the two sides. Respiration was thoraco-abdominal in type. Tactile fremitus was normal throughout the entire chest. There was hyperresonance throughout. The breath sounds were roughened with a few râles found in the upper right anterior part of the chest. Coarse vibrating rhonchi were heard throughout. There was no cardiac impulse visible or palpable. The borders of the heart could not be made out. The heart sounds were distant. No distinct sound could be heard. The radials were equal, full and regular, with a rate of 96 per minute. There was no palpable tumor mass. There was some muscle rigidity of the abdomen,

2. Warthin: Contributions to Medical and Biological Research Dedicated to Sir William Osler, New York, Paul B. Hoeber, 1919, p. 1042.

3. Bezancon, F.: La Presse Medicale, **28**:885, 1920.

but this was more voluntary than involuntary. Examination of the genitalia was negative, as were the neuromuscular and joint examinations.

Laboratory Findings.—The blood count revealed: 6,920,000 red blood cells; 11,100 white blood cells, 79 per cent. of polymorphonuclears and 21 per cent. of mononuclears. Urinalysis revealed: specific gravity, 1.008; acid; clear; straw color; free from sugar; trace of albumin. Throat culture showed staphylococcus and streptococcus. The throat smear was negative for Klebs Löffler bacillus. There were many pus cells. Sputum examination was negative for tubercle bacilli. It showed free red blood. The blood Wassermann test was negative. There were 37.5 mg. noncoagulable nitrogen per 100 c.c. of blood and 55.1 per cent. by volume of carbon dioxid.

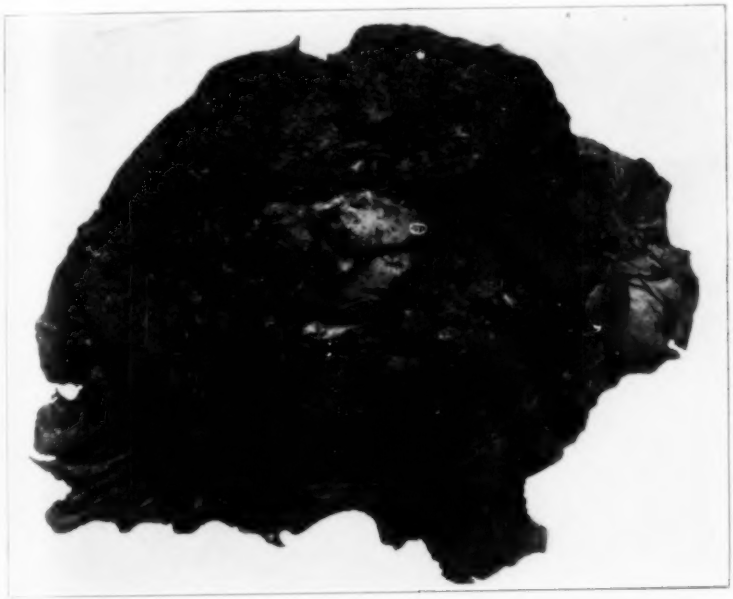

Fig. 2.—Extreme pulmonary anthracosis with cavitation.

Roentgen-Ray Report.—A fluoroscopic study was made of the chest. No definite deformity of the heart shadow could be demonstrated. The size of the shadow was within the normal limits. Definite accentuation of the root shadows was noted, also prominent linear markings and some diffuse parenchymal infiltration. The appearance of the fluoroscopic picture was not that of a circulatory pathologic condition.

Roentgenograms were made of the chest. There were extensive root shadows, with the deposit largely diffuse on the left side and in part calcified on the right. There were also some calcified masses in the lower part of the right lung and in the parenchyma adjacent to the left root. There were prominent linear markings as described in the fluoroscopic notes. The roentgenologist concluded that the findings were those of a chronic infection or changes incident to dust inhalation. The patient said he was a coal worker and this occupation could account for most of the lung changes.

Comment.—It will be noted that this case differs from typical cases of sclerosis of the pulmonary artery in the absence of the peculiar changes in the cardiac roentgenographic shadows emphasized by Warthin.

Case 2.—*History.*—A man, aged 48, a coal miner, entered the hospital on March 15, complaining of dropsy, cough and pain in the chest. He had had this trouble for six months. The family history was negative. The patient had had pneumonia at 20 years of age; otherwise he had never been sick in bed until six months before, when he caught a bad cold, and he had coughed ever since. At that time he weighed 180 pounds (81.6 kg.) and was very well and strong, but since then he had gradually lost weight, until he was markedly emaciated and too weak to walk. He had drunk heavily until three years ago.

Physical Examination.—The patient was a man of middle age, large of frame, but markedly emaciated. He was propped up in bed and was markedly dyspneic. There was general cyanosis, especially marked in the upper portion of the body; the lips and ears were deep blue-black; the conjunctivae were dark beefy red. He coughed almost continually and expectorated large quantities of purulent sputum colored with bright pink blood. The pupils reacted normally. The tongue was heavily coated, and the teeth were in very poor condition. The veins of the neck pulsated markedly, and the cervical glands were palpable.

The chest was of the emphysematous type, and there were numerous distended venules over its anterior aspect. Expansion was equal on the two sides. There was well marked tactile fremitus with a hyperresonant percussion note throughout. Moist and musical râles and coarse rhonchi were heard over all the lung areas, front and back. The heart could be outlined by percussion. No apex beat could be seen. Only a faint first sound was heard at the nipple. In the aortic and pulmonic areas the first and second sounds could be heard and were of normal quality. At the ensiform and 2 inches to the right of the sternum in the sixth interspace a long blowing systolic murmur was made out. The liver was felt to extend one hand's breadth below the right costal margin and was tender. The spleen was not felt. There was marked edema of both legs. (During the patient's stay in the hospital ascites and edema of the scrotum developed.)

Laboratory Findings.—Blood count revealed: hemoglobin, 95 per cent. (?) (Talquist); leukocytes, 7,400; polymorphonuclears, 78 per cent.; small lymphocytes, 16 per cent.; large lymphocytes, 6 per cent.; red cells 6,360,000. No abnormalities were noted in the stained smear. Blood pressure was: systolic, 130, diastolic, 80. The urine contained a trace of albumin and an occasional granular cast. In the sputum were pus and "heart failure" cells. No tubercle bacilli, eosinophilia or spirals were found.

Roentgen-Ray Examination.—Examination of the chest revealed: extensive infiltration of both lungs below the clavicle, a wide mediastinal shadow and rotation of the heart shadow. The roentgenograms suggested advanced tuberculous infiltration of the lungs and aortitis.

Because of the dense shadow at the base of the heart a clinical diagnosis of mediastinal tumor had been made. The patient died on May 3 with signs of cardiac failure.

Necropsy.—The body was that of a man past middle age, and poorly nourished. General anasarca was present, especially of the lower limbs. There was bluish back suggillation on the inner side of the right leg. The chest was barrel shaped. Petechial spots covered the thorax. There was marked cyanosis of the face and neck.

On section it was found that a clear amber ascitic fluid filled the entire abdominal cavity. The peritoneum was normal; the panniculus was scanty. The muscles were pale and watery.

The dome of the diaphragm was in the fourth interspace on the right and the fifth on the left.

The liver was four fingerbreadths below the ribs in the parasternal line. Superficial inspection of the abdomen was negative.

The right pleural cavity contained no fluid. The left pleural cavity was full of dark amber fluid. There were old adhesions on the left lung which was retracted from the chest. There were old adhesions at the base. The pericardium was adherent to the sternum in front.

Fig. 3.—Cardiac dilatation and pulmonary fibrosis in a patient with a positive Wassermann reaction.

The apex of the heart was the fifth rib outside of the nipple line. The pericardium contained 200 c.c. of clear amber fluid.

The right lung adhered to the base behind by old adhesions. The heart was dilated. The right ventricle had chicken fat clot extending into the pulmonary artery. The tricuspid ring was dilated; the tricuspid valves were negative. The right auricle was empty. The ear of the auricle had a small postmortem clot; the left ventricle had a small amount of postmortem clot.

The mitral valve admitted two fingers with ease. A small postmortem clot was tangled in the mitral flap. The first part of the aorta showed linear sclerosis. The muscle of the left ventricle was normal.

The right lung was voluminous. The pulmonary vessels were dilated and thin walled, but no other gross lesion of the pulmonary artery was noted.

Both lungs were slate-like in color (Figs. 1 and 2) and were uniformly gritty on cut section. When handled, coal black rubbed off on the prosector's fingers. There were numerous cavities from 1 to 5 cm. in diameter in both upper lobes formed by the breaking down of atrophic alveolar septums. There was a mucopurulent discharge streaked with black in all the bronchi. The mediastinal lymph nodes were large and jet black, but no tubercles were discovered in them. The lung was full of small hard black nodules throughout. The pulmonary artery was empty. The left lung was covered with fibrinous exudate under which were areas of yellow thickened pleura. Large cavities in the left lung were hollowed out by breaking down the anthracotic lung tissue. There was no lesion of the pulmonary artery.

The spleen was smaller than normal. The capsule was thickened. There was diffuse darkening of the pulp. Malpighian bodies were not visible.

The left suprarenal was larger than normal. On section the medulla was found to be prominent. The left kidney showed depression of the upper pole. The cut surface appeared congested. There were no gross changes of importance. The right kidney was normal in size. On section it appeared to be congested. The right suprarenal also was larger than normal.

The liver was smaller than normal. There was a whitish scar on or near the right edge. Fatty change and congestion were found on section; there was no increase in the connective tissue.

The pelvis was normal.

The appendix was retrocecal, bound down by adhesions.

Diagnosis: Anthracosis of the lung and cavitation; emphysema, cardiac dilatation.

Comment.—This case resembled Ayerza's disease clinically more than the first one, because of the broadening of the base of the cardiac shadow. The significant features are the history of coal mining and the roentgen-ray evidence of pulmonary fibrosis. The aortitis and tuberculosis suggested by the roentgen ray were not confirmed by postmortem examination. The pathologic condition was such, however, as to make it indistinguishable from tuberculosis roentgenologically. The cavitation due to breaking down of coal dust laden septums in the lung parenchyma was striking. Here again we have the syndrome of cyanosis, dyspnea and polycythemia with chest findings indistinguishable from true Ayerza's disease but due to extensive anthracosis.

Case 3.—*History.*—A man, aged 42, a laborer, entered the hospital on account of dyspnea, cyanosis, cough and expectoration. His past history was characterized by frequent and repeated acute infections, including scarlet fever, smallpox, measles, whooping cough and malaria. He had been in the hospital for two weeks two years ago for "kidney trouble." He had had "asthma" for ten or twelve years, associated with "kidney trouble," and he had had gonorrhea twenty years ago. His social and marital histories were negative. He had five children alive and well. His family history was negative. Six weeks before entering the hospital his asthma became worse and marked cyanosis and swelling of the extremities was noticed. He began to expectorate large quantities of blood tinged sputum.

Physical Examination.—The patient was propped up in bed and markedly dyspneic and cyanotic. His face and neck were especially cyanotic, and the conjunctivae were a dark beefy red. The pupillary reactions and ocular movements were normal. The ears and nose were normal. The tongue was coated, and the teeth were in a bad condition with numerous cavities and extensive pyorrhea. No pulsations were noted in the neck.

Fig. 4 (Case 4).—Early stage of pulmonary fibrosis.

The chest was barrel shaped and emphysematous. Respiratory excursion was increased and the accessory muscles of respiration brought into play. The apex beat was not seen. On percussion the cardiac borders were not accurately made out because of hyperresonant lung sounds. Auscultation revealed heart sounds of normal quality and rhythm, and many musical râles and coarse rhonchi were heard throughout the chest. The abdomen was negative to the usual methods of physical examination. There was marked edema of the feet. Neuromuscular and joint examination was negative.

Laboratory Findings.—Urinalysis revealed a trace of albumin with a few granular casts. The blood count revealed: red cells 7,700,000; white cells, 7,600; polymorphonuclears, 80 per cent.; small mononuclears, 16 per cent.; large mononuclears, 4 per cent.; hemoglobin, 100 per cent. The smear showed an occasional nucleated red cell.

Roentgenologic Report.—The chest findings were: The heart was considerably enlarged through the ventricles, especially the left. There was marked density shown at the hilum of the lung on both sides. The aortic shadow was not widened. The shadow of the hilum was considerably enlarged on the right, and there was diffuse fibrosis of both lungs. The blood Wassermann test was positive.

Treatment and Course.—During the next week the patient exhibited no change of condition except marked lethargy and somnolence. The man was given vigorous mixed treatment and left the hospital slightly improved. He then disappeared from observation.

Comment.—It is evident from examination of Figure 4 that the major pathologic rôle in this case was probably played by the heart. The amount of pulmonary fibrosis, while marked enough to be mentioned by the roentgenologist, was not thought to be as important as the cardiac finding.

This is an example of a case in which the diagnosis is in doubt as regards the nature of the underlying lesion. The positive Wassermann test along with the long history of "asthma" is suggestive of a syphilitic basis for the cardiac injury, but a lesion of the pulmonary artery could not be proved.

Case 4.—*History.*—A woman, aged 32, married, entered the hospital on account of dyspnea and cyanosis which had been present for the past three months. The family and marital histories were negative. She had had the usual childhood diseases and pneumonia at 11 years of age, with good recovery. She had had no other illnesses. She had never had a sore throat. For some months past, the patient had noticed gradually increasing breathlessness on exertion. She had passed through two normal pregnancies. She had had acute appendicitis early in her second pregnancy and had been operated on, with good recovery.

Physical Examination.—A fairly well nourished young woman was lying in bed. There was marked pallor of the skin, but the lips, face and extremities showed marked cyanosis. The venules over the anterior thorax were prominent. The breathing was rapid and deep as though the patient had recently been running, but no respiratory obstruction appeared to be present. There was a slight cough and a moderate amount of sputum. The apex beat was seen in the fifth interspace within the nipple line. The heart rate was 104 and the respiration 34. Percussion revealed cardiac dulness extending to the nipple line and normal resonance throughout the chest. Auscultation revealed rapid heart sounds, abnormal in quality. No murmurs were heard. The breadth sounds were rather harsh but vesicular in quality, and no areas of consolidation were made out. There were a few dry râles at the apexes. The abdomen and extremities were negative. Neuromuscular and joint examination was negative. Laryngeal examination was negative. The tonsils were enlarged with cheesy detritis in crypts. Sputum examination revealed a few leukocytes and streptococci. The patient did not have a rise in temperature while in the hospital.

Laboratory Findings.—Blood examination revealed: red blood cells, 5,920,000; white cells, 14,700; polymorphonuclears, 78 per cent.; small mononuclears, 10

per cent.; large mononuclears, 11 per cent.; eosinophils, 1 per cent. The blood Wassermann test was repeatedly negative. Urinalysis was negative.

Roentgenologic Examination.—Examination of the chest gave rise to some controversy. One roentgenologist interpreted the findings as indicating mediastinal tumor; two others held that the picture was that of pulmonary fibrosis of nontuberculous character, and the medical director of a large sanatorium for

Fig. 5 (Case 4).—Late stage of pulmonary fibrosis.

the care of tuberculous patients, after seeing several films of the chest and examining the patient repeatedly, said that in his opinion the condition was tuberculous.

A large number of chest films were made over a period of two years and showed all stages from diffuse fibrosis of moderate grade to intense opacity at the mediastinum and bases, so that just before death the diagnosis of neoplasm seemed more probable, although the roentgenologists who took the plates insisted that the condition was not neoplastic but inflammatory in nature (Figs. 4 and 5).

Diagnosis: Several clinical diagnoses were made by various consultants, among them pulmonary tuberculosis, mediastinal tumor, lymphosarcoma of the bronchial glands and diffuse pulmonary fibrosis due to infection of unknown origin. The outstanding features were as noted, dyspnea, cyanosis and polycythemia without evident gross intrathoracic pathology to account for the syndrome until the roentgen-ray findings shortly before death revealed the marked pulmonary fibrosis.

Necropsy.—The body was that of a fairly well nourished woman about 20 years of age. The skin was pale, with marked cyanosis of the lips and finger tips. There were no external markings of importance. Necropsy permission was limited to examination of the thorax. On opening the thorax we found the thymus persistent but not enlarged and extending down to the ear of the right auricle. The pericardium was normal. The tissues of the anterior mediastium were thickened and contained lymph nodes which were somewhat enlarged and on section showed definite inflammatory reaction. No tubercles or neoplastic process was found. The heart was definitely hypertrophied. There was well marked sclerosis of the first portion of the aorta and definite sclerosis of the first portion of the pulmonary artery. The sclerosis was nonspecific in type. Both lungs were uniformly hard and on removal were found to be small and dense. They were uniform externally and presented no nodules or localized areas of infiltration. The condition of the whole lung resembled that of a diffuse unresolved pneumonia. There was uniform increase of the connective tissue extending out from the bronchial tree to the cortex. No tuberculous process was present.

Microscopic examination showed diffuse round cell infiltration of the lung parenchyma accompanied by a uniform productive pneumonitis.

Diagnosis: Chronic infectious pneumonitis, chronic mediastinitis, pulmonary fibrosis, secondary symptomatic polycythemia.

Comment.—The point of entry of the infection in this case is unknown, but it is assumed to be the tonsils since they were reported grossly pathologic by the laryngologist. The case differs from the others in several particulars. There was no orthopnea even when the dyspnea was at its worst. The breathing was of a peculiar rapid quality resembling that of a runner rather than labored and difficult as is usual in these cases. The cyanosis was confined to the lips and finger tips, and the face was not suffused or the conjunctivae injected. The white count showed a distinct reaction to infection in spite of absence of fever, although this phenomenon might well have been considered, and was indeed so interpreted by one consultant, as being due to neoplastic extension with breaking down of the immune processes against malignancy.

The microscopic picture was that of active diffuse pneumonitis with extensive round cell infiltration and thickening of the alveolar septums due to proliferation of young fibroblasts. There was distinct alveolar catarrh, with desquamation and proliferation of the alveolar epithelium. There was no lesion of the branches of the pulmonary artery (Figs. 6 and 7).

COMMENT

It is evident that the syndrome described above depends on the pulmonary fibrosis caused in two cases by coal dust and in the third and fourth by irritation and infection of unknown origin. In none of them were the lesions of the pulmonary artery significant. In a fifth case there was extensive pulmonary arterial syphilis unaccompanied by the Ayerza syndrome because of the absence of the necessary degree of pulmonary fibrosis. This case was one of aortic aneurysm in which

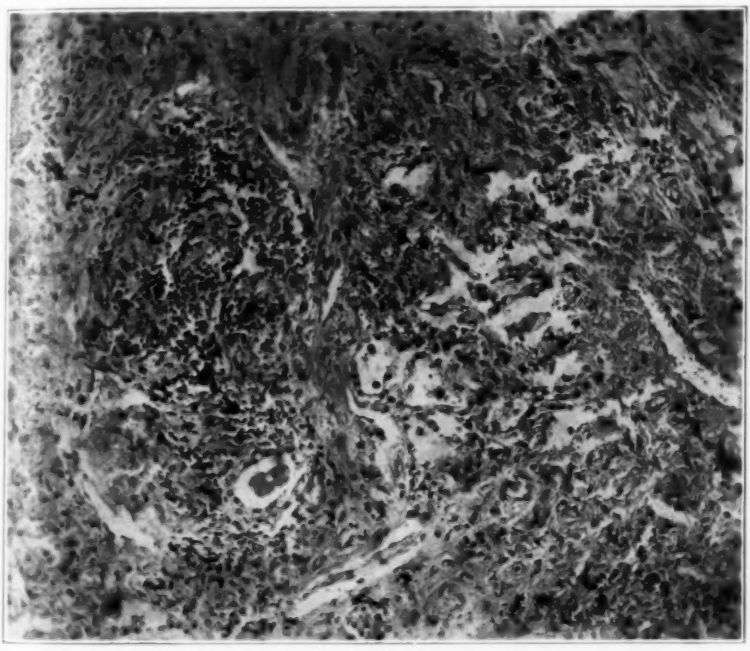

Fig. 6 (Case 4).—Diffuse pneumonitis with fibrosis.

death was due to rupture into the pleural cavity. At the postmortem examination, extensive syphilis of the pulmonary artery was found besides the lesion in the aorta. The condition was relatively active and recent, with patchy areas of fibrosis in the lung interspersed with large amounts of relatively normal lung parenchyma. The case history and physical findings are not given in detail because the case did not resemble the other ones in any way clinically. There was no cyanosis and dyspnea, and a moderate anemia was present instead of an erythremia.

The development of the polycythemia in the first four cases is easily understood and was a prominent feature of all of them. Legge [4] has recently reported that the syndrome caused by inhalation of quartz dust by gold miners is unaccompanied by polycythemia but is especially characterized by marked anemia. Apparently the anemia must be explained by other factors at work in these cases besides the pulmonary irritation, because the pulmonary pathology per se would tend to produce the opposite effect. Pulmonary fibrosis in general due to whatever cause tends to produce erythrocytosis, unless other factors prevent its development.

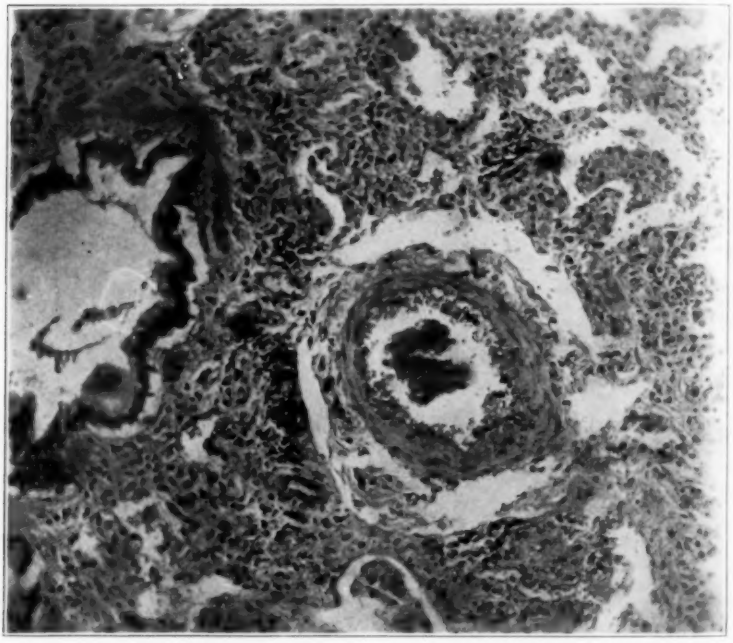

Fig. 7 (Case 4).—Diffuse pneumonitis with fibrosis and alveolar catarrh.

SUMMARY

Five cases are reported, four of which present clinical features closely resembling Ayerza's syndrome but due to pulmonary fibrosis rather than primary disease of the pulmonary artery. The fifth case illustrates the fact that extensive pulmonary arterial syphilis may occur without Ayerza's syndrome.

4. Legge, Robert T.: Miners Silicosis, J. A. M. A. **81**:809 (Sept. 8) 1923.

DIRECT BLOOD-STREAM INFECTION THROUGH THE TONSILS *

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"Do the tonsils show any peculiar anatomical structure or possess any specific physiology or undergo pathologic changes that would make them more liable to act as a gateway of infection than other structures in the body?" [1] The histologic factors in chronic tonsillitis are: (1) loss of epithelium on the surface or in the crypts; (2) the presence of masses of keratinized epithelial cells in the crypts; (3) hyperplasia of endothelial cells; (4) accumulation of plasma cells, lymphocytes and leukocytes around the margin of the crypts; (5) evidence of hemorrhage in the parenchyma or in the lumen of the crypt; (6) the presence of polymorphonuclear cells and lymphocytes in the epithelium lining the crypts; (7) the presence of bacteria in the crypt epithelium and in the parenchyma of the tonsil (probably in lymph channels or blood vessels); (8) thickening of the capsule and increased fibrosis of the trabeculae. In every case of acute tonsillitis and in a majority of those with a chronic tonsillitis, the lymph glands of the deep cervical group near the angle of the jaw are palpably or visibly enlarged, and suggest that the portal of entry is through the lymphatics.

In a previous publication,[2] in 1916, I insisted that the tonsils or adenoids could not be responsible for a general systemic disturbance, such as infectious arthritis, unless there was a palpable enlargement of the lymph glands in the neck; and for many years such patients were advised that there was no indication for an operative removal of their tonsils or adenoids. Many of these patients, however, subsequently informed me that after leaving the Johns Hopkins Hospital they consulted another physician who advised a tonsillectomy, and that soon after the operation their symptoms began to improve and ultimately they were cured. This stimulated us again to study histologically our collection of tonsils and adenoids (removed from 3,000 patients during the

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* Presented before the Medical Society of the Johns Hopkins Hospital in November, 1923.

1. Wood, G. B.: Dangers of Tonsillectomy, Am. J. M. Sc. **154**:88 (Aug.) 1917.

2. Crowe, Watkins and Rothholz: Relation of Tonsillar and Nasopharyngeal Infections to General Systemic Disorders, Bull. Johns Hopkins Hosp. **28**:1-63 (Jan.) 1917.

past ten years) in order to see whether we could demonstrate a direct infection of the vascular system.

Our first encouraging finding was the fact that the epithelium on the surface and the epithelium lining the crypt differ markedly in their

Fig. 1.—Section of a normal tonsil, showing the difference between the epithelium on the surface and that lining a crypt: *a*, lumen of crypt; *b*, lymph follicle; *c*, epithelium on oral surface; *d*, epithelium lining a crypt. The rich blood supply of the crypt epithelium may be noted.

blood supply. Figure 1 shows the appearance of a normal crypt. The epithelium here has papillae similar to those in the skin, and, like the skin, is rich in capillaries. A complete absence of or a marked hyalinization of the epithelium lining the crypts is the most common finding in

tonsils removed at operation. It is uncommon to find any changes in the epithelium on the surface of the tonsil. (Fig. 2). This suggests that the destruction or localized ulceration of the epithelium in a crypt (as shown in the remaining illustrations) is associated with a thrombosis of the blood vessels that are normally present in this epithelium.

These findings suggest that the general systemic disturbances associated with a chronic tonsillitis or a chronic nasopharyngitis may be due

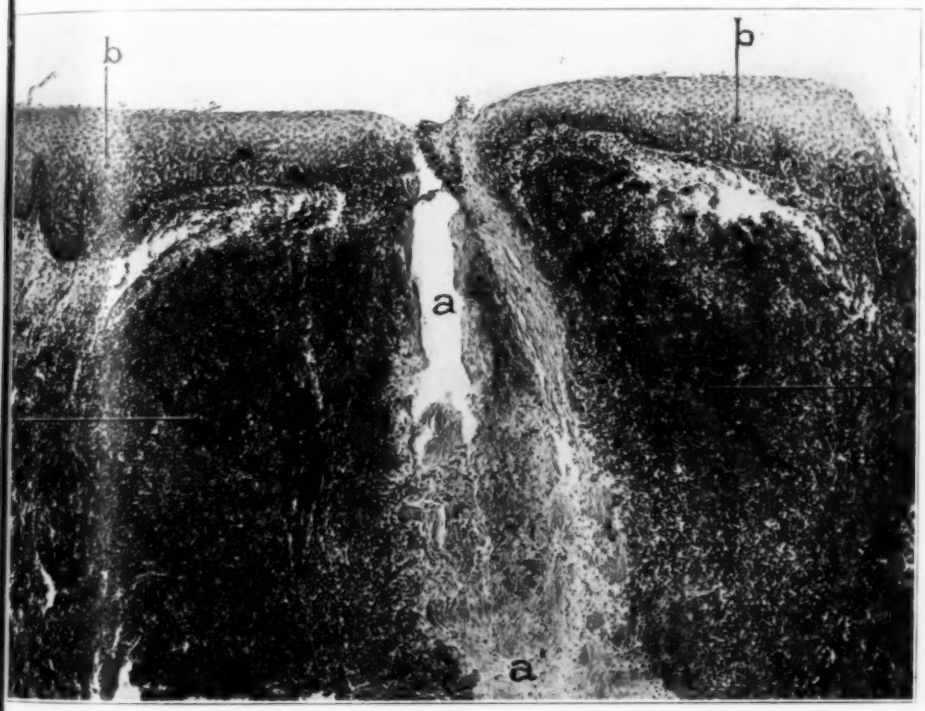

Fig. 2.—Section of a chronically infected tonsil: *a*, *a*,' lumen of crypt partially filled with cellular débris and inflammatory cells. The complete destruction of the epithelial lining of the crypt may be noted; *b*, epithelium on the oral surface, thickened but otherwise normal; *c*, accumulation of plasma cells, lymphocytes and leukocytes around crypt.

to direct blood-stream infection. The destruction of the epithelium lining the crypt may be acute and widespread, and if there is good drainage from the crypt into the oral cavity the ulcerated area may heal rapidly. If an ulceration of the epithelium occurs in a crypt in which there is a stricture at the orifice, the resulting accumulation of cellular débris and bacteria prevent healing, and a chronic ulcer results, with

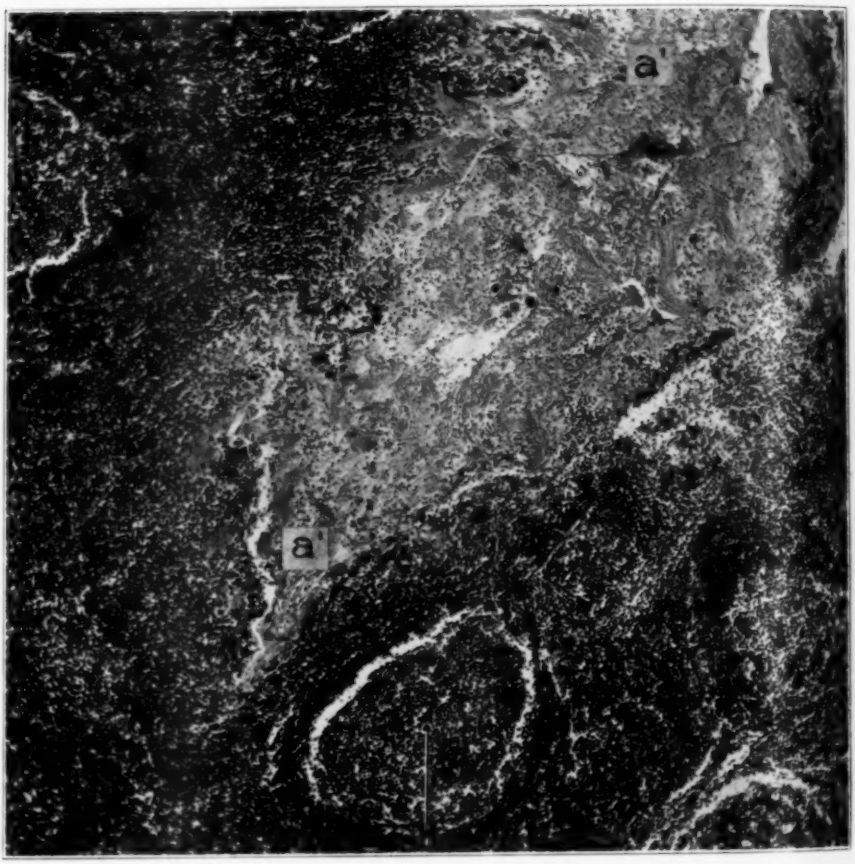

Fig. 3.—The bottom of the crypt shown in Figure 2: *a*, lumen of crypt filled with débris; *b*, germinal centers. The absence of the lining epithelium may be noted.

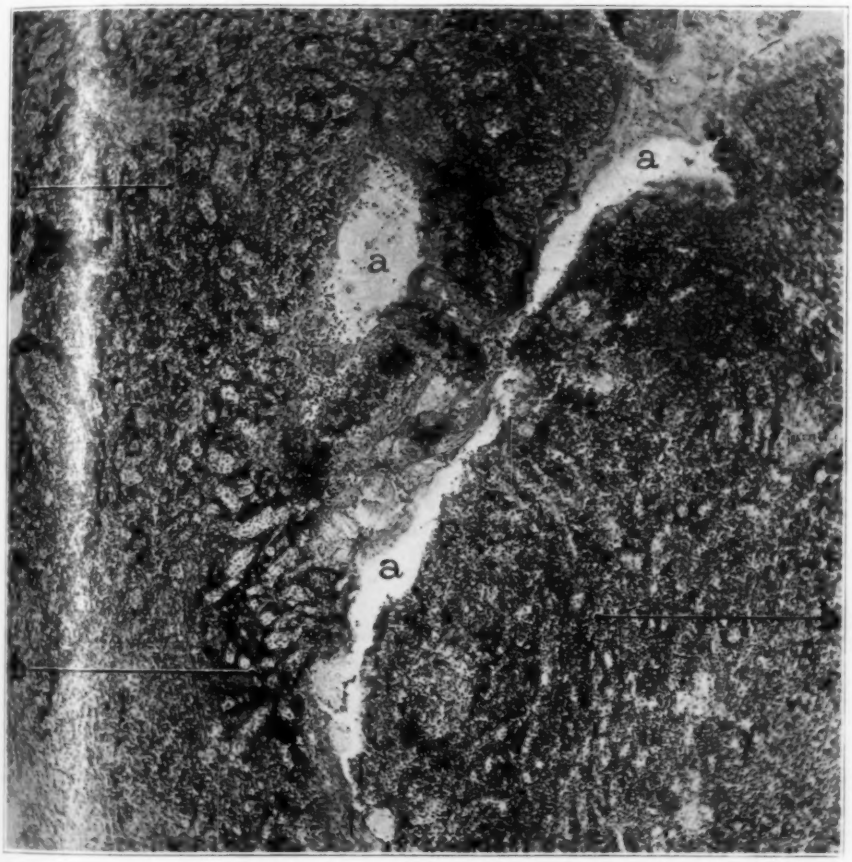

Fig. 4.—A common finding in chronic tonsillitis: *a*, lumen of a crypt. The absence of lining epithelium may be noted. A rich network of capillaries surround the crypt on all sides. Under a higher magnification, red blood cells are seen in each of the areas indicated by *b*.

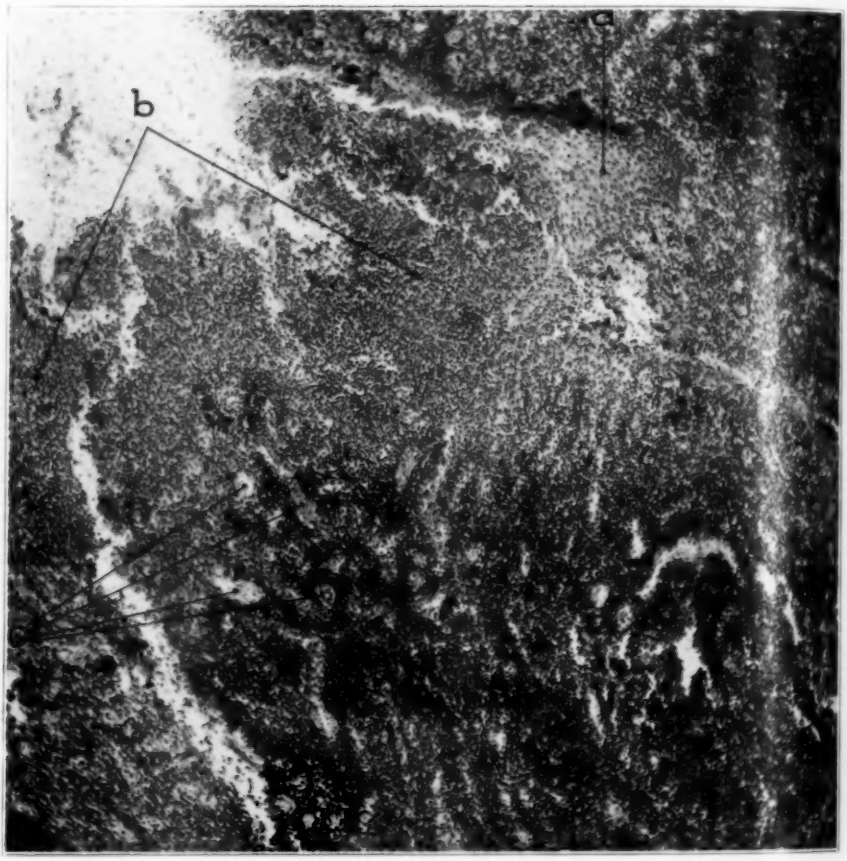

Fig. 5.—The bottom of a crypt with a localized chronic ulceration. This tonsil was removed as a possible focus that was causing an infectious arthritis, with a clinical recovery. *a*, remains of epithelium lining the crypt; *b*, inflammatory cells in bed of an ulcer; *c*, rich network of capillary blood and lymph channels in bed of ulcer.

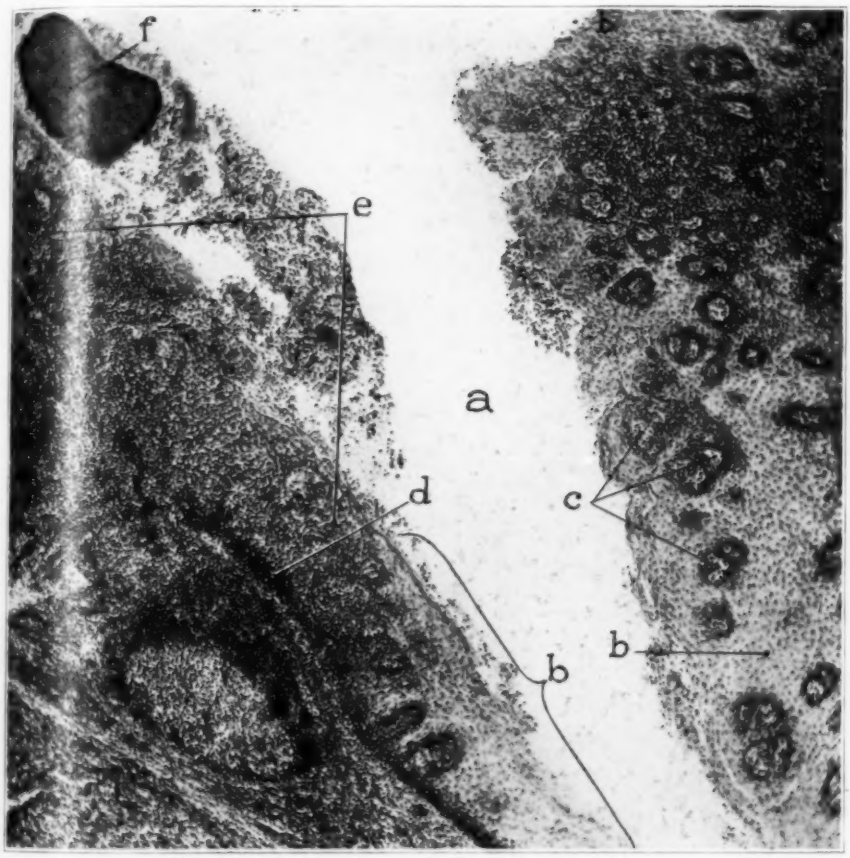

Fig. 6.—Section of a tonsil removed for infectious arthritis, with a clinical recovery; *a*, lumen of crypt; *b* to *b*, normal epithelium lining crypt; *c*, capillaries containing red blood cells; *d*, inflammatory cells in the base of an ulceration; *e*, area of destruction of epithelium; *f*, a clump of bacteria and cellular débris in lumen of crypt.

an exceptionally rich network of blood vessels in its base. It is easy to imagine, but difficult to prove, that from time to time emboli containing bacteria enter the blood stream direct, in addition to those that gain entrance through the large lymphatic channels in the tonsil.

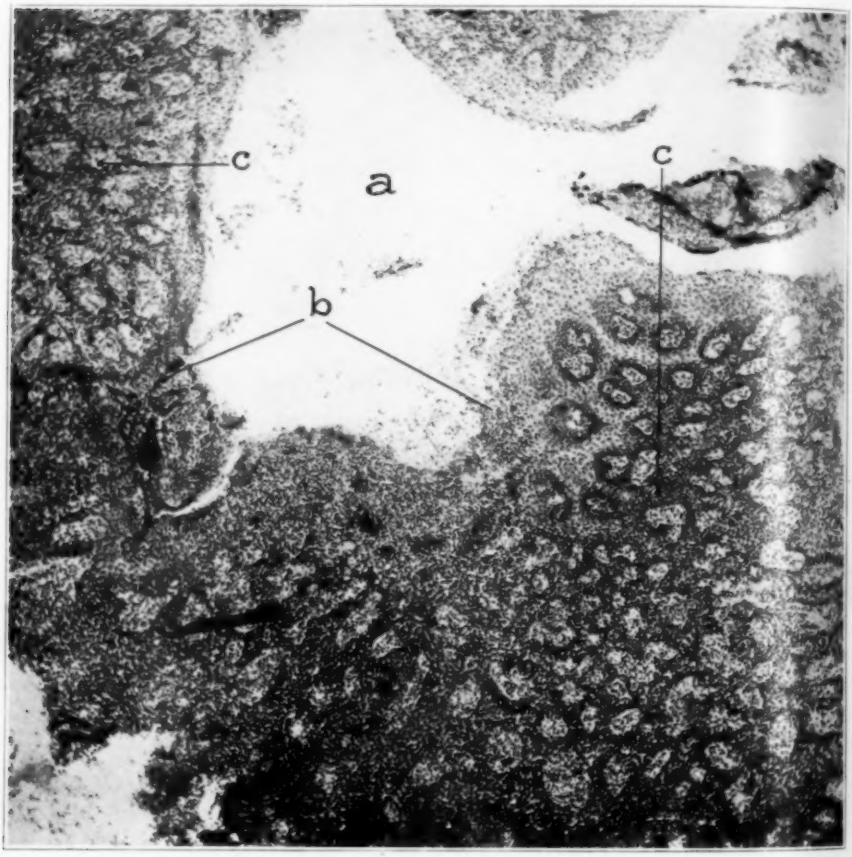

Fig. 7.—Localized ulceration in a crypt. Tonsil removed from a patient with infectious arthritis, with a clinical cure. *a*, lumen of crypt; *b*, area of ulceration; *c*, normal crypt epithelium.

It is well known that in many cases of infectious arthritis a hemolytic streptococcus may be cultivated from a gland removed from the groin, the popliteal space, the axilla or the neck. Blood removed from an arm vein in such cases rarely contains organisms, but it is possible that if blood were removed from the jugular vein a positive culture might

result in those cases in which the focus of infection is located in the upper respiratory passages.

It also seems reasonable to suppose that a careful microscopic search might disclose ulcerations in the lymphatic tissue in the intestinal

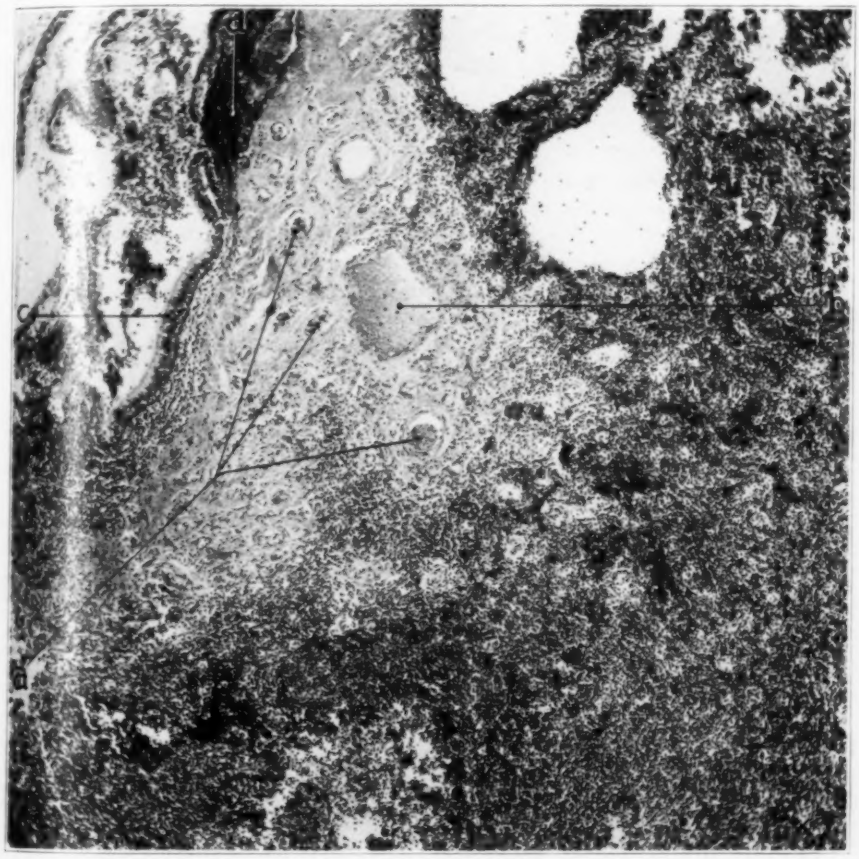

Fig. 8.—Chronic infection of the lymph-adenoid tissue in the nasopharynx. A chronically infected nasopharynx is of equal importance with the tonsil as a focus of infection. *a*, small arteries containing thrombi; *b*, a normal vein filled with blood; *c*, ciliated epithelium lining a crypt; *d*, accumulation of inflammatory cells.

wall similar to those that occur in the crypts of the tonsils. A digestive disturbance is usually associated with every acute infection and with many chronic infections of the tonsils, adenoids and accessory nasal

sinuses. It is possible that the lymphoid tissue of the intestinal tract is infected with the swallowed discharge. In children, particularly, a colon bacillus pyelitis frequently follows an acute upper respiratory infection. Whether this is due to an exacerbation of a low grade chronic infection in the urinary tract or to a hematogenous infection is not known.

SUMMARY

The epithelium lining the crypts of the tonsil differs from that covering the surface. The crypt epithelium has papillae and a rich network of capillaries, while the epithelium covering the surface of the tonsil has but few capillaries and no papillae. A destruction of the crypt epithelium, in whole or in part, is the most common pathologic finding in chronic tonsillitis. In the majority of the tonsils examined microscopically, the ulcerated areas in the crypts have healed; in others there are definite chronic ulcers.

These ulcerated areas are surrounded by an accumulation of plasma cells, lymphocytes and leukocytes. There is a rich network of thrombosed capillaries and lymph channels around the margins of the ulcers, and the conditions seem favorable for the passage of organisms into the lymphatic system and the liberation of infected emboli into the blood stream. We have found such ulcerated areas most frequently in the tonsils of individuals suffering from infectious arthritis, and least frequently in those in whom the tonsils were removed for acute rheumatic fever and chorea. A few of the arthritic patients whose tonsils show histologic ulcers in the crypts have no palpable enlargement of the cervical lymph glands, and the findings in these cases suggest a direct blood stream infection. This supposition is strengthened by the fact that this type of lesion in the crypt is found most commonly in patients with a variety of arthritic involvement (infectious arthritis) that responds most frequently to the removal of an infected focus and general hygienic measures.

HISTOLOGIC HYDROGEN-ION STUDIES OF THE KIDNEY *

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Studies of nephritis and renal function have included much work on the blood and urine, especially that done in connection with hydrogen-ion concentrations. They have included little work on the secreting cells, however. The present studies were undertaken in an attempt to determine what parts of the uriniferous tubules are responsible for an acid or alkaline reaction of the urine. It was felt that the localization of such determining function would yield data of value concerning the normal and pathologic physiology of the kidney. The hydrogen-ion concentrations in the secreting cells and in the urine were determined simultaneously under varying conditions. The following phases of the problem have been considered: 1. Where is the reaction of the urine determined? 2. How is it determined? 3. What effect has altering the reaction of the urine on the normal findings? 4. What effect has nephritis on the normal findings? 5. What effect has alkali therapy on the findings in nephritic kidneys? These investigations were carried out by the use of vital indicator dyes introduced into the living animal.

In 1885, Dresser [1] used dyes in vivo for their indicator reaction, injecting acid fuchsin into frogs. In an acid solution the dye is red; in alkaline, yellow. He found that following an injection of acid fuchsin the urine became brilliantly red, but no red cells were demonstrable in the kidney. After repeated injections the cells of the convoluted tubules and the straight tubules became red. Fischer [2] explains this on the basis that repeated injections of acid fuchsin, which is a weak acid, injure the cells and thus cause an acid reaction. Dresser also found the cells stained red when the renal artery was tied, and the cells asphyxiated. Nussbaum [3] and Heidenhain,[4] working with indigosulphonate, obtained essentially similar results. Grützner [5] found that the glomeruli could also be stained with indigosulphonate, showing an acid reaction, when sufficient asphyxia was produced in the kidney. These results and Fischer's conclusions are essentially in accord with those described below.

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* From the Hull Laboratory of Anatomy and the Hull Laboratory of Physiology, University of Chicago.

1. Dresser: Ztschr. f. Biol. **21**:41, 1885. Ibid., **22**:56, 1886.
2. Fischer: Edema and Nephritis, New York, John Wiley & Sons, 1915.
3. Nussbaum: Pflüger's Arch. **16**:141, 1878.
4. Heidenhain: Pflüger's Arch. **9**:1, 1875.
5. Grützner: Pflüger's Arch. **24**:461, 1882.

Harvey and Bensley,[6] Edinger,[7] Fränkel [8] and others have used similar indicator dye methods in connection with the secretion of hydrochloric acid or its precursor by the gastric mucosa. Harvey and Bensley used neutral red successfully, and Edinger sodium alizarinate. Hoeber [9] and Sörensen [10] give excellent discussions on indicatory dyes as applied to physiologic work. Marshall and Vickers,[11] in studying the renal secretion of phenolsulphonephthalein, observed the dye in the convoluted tubules of the kidney of the dog.

METHODS

The first problem which presents itself in undertaking to determine intracellular hydrogen-ion concentrations by means of vital indicators is the choice of the dyes. An indicator to be of use must fulfil all the following conditions: It must be nontoxic; it must be readily absorbed by living cells and therefore be soluble in tissue fluids; it must

Nature of Color Changes and Hydrogen-Ion Concentrations at Which These Occur

Dye	Acid			Alkaline		
	P_H	Color	Relative to H_2O	P_H	Color	Relative to H_2O
Neutral red	$10^{-6.8}$	Red to blue	Neutral (P_H 10^{-7})	10^{-8}	Orange to yellow	Alkaline
Sodium alizarinate	10^{-5} 10^{-8} 10^{-10}	Yellow Orange Magenta	Acid Alkaline Alkaline	10^{-12} 10^{-14}	Purple Blue	Alkaline Alkaline
Azolitmin	10^{-6}	Pink	Slightly acid	10^{-7} 10^{-8}	Violet Blue	Neutral Slightly alkaline

show a marked, readily detected color change; and last, the end-point must be at a hydrogen-ion concentration within the range of the changes in living cells. The last requirement is the most essential one.

Three dyes were found to be of great value and were used in this series of experiments. Several dyes were tried and discarded, especially because the end-point of color change was at too high a hydrogen-ion concentration. For example, Congo red, methyl red, and dimethylamidoazobenzol have end points between $p_H 10^{-3}$ and $p_H 10^{-6}$, so that they give an akaline reaction in pure distilled water. Binschädler's green was useless because of its toxicity. The three dyes used successfully were neutral red, sodium alizarinate and azolitmin.

6. Harvey and Bensley: Biol. Bull. **23**:225, 1912.
7. Edinger: Arch. mikro. Anat. **17**, 1879.
8. Fränkel: Arch. f. d. ges. Physiol. **48**:63, 1891.
9. Hoeber: Physikalische Chemie der Zelle u. Gewebe, 1914, pp. 170-173.
10. Sörensen: Biochem. Ztschr. **21**:131 and 304, 1909.
11. Marshall and Vickers: Bull. Johns Hopkins Hosp. **34**:1, 1923.

Azolitmin has the same color changes as litmus, and can be obtained as a pure dye. It changes color at the same level as neutral red, about $p_H 10^{-7}$, or at the true neutral point of pure distilled water. Sodium alizarinate is somewhat less satisfactory. It is difficult to obtain uniformly pure alizarin. Sodium alizarinate is soluble and purple in color; on the addition of acid, the more insoluble alizarin is precipitated as an orange dust. The sodium salt was prepared (KR.8,36) from alizarin by the addition of sodium hydroxid to an excess of the alizarin dye, and the filtrate used. These three dyes are nontoxic, are readily soluble in water, are absorbed by the cells and secreted into the urine. Throughout the recorded results the terms acid or alkaline are used relative to the p_H of pure distilled water at 10^{-7}.

Intravenous injection of concentrated solutions of the dyes was found to be the most satisfactory method of administration. Perfusion with dilute solutions introduced several sources of error, by asphyxia of the kidney and altering the normal physiologic state. The animals used were rabbits, dogs and a few white mice. In the latter, subcutaneous injection of the dyes was resorted to. Rabbits were used, first, to determine the efficiency of the dyes and, secondly, because they have a normally alkaline urine in contradistinction to the acid urine of the omniverous dog. It is essential that the kidneys be examined immediately after death, because about five minutes after death the reaction of the tissues begins to change as a result of anutolysis.

RESULTS

The hydrogen-ion concentration in the kidney cells and urine were determined in thirteen normal rabbits by the use of the three dyes mentioned above. The results in all these experiments are essentially identical, and the protocol of one representative experiment will suffice:

EXPERIMENT KR. 33.—Fifteen cubic centimeters of a saturated filtered solution of azolitmin in distilled water was injected into the marginal ear vein of a male rabbit, weighing 1,300 gm., without any apparent toxic effect. A few drops entered the subcutaneous tissue, where the purplish color became blue (alkaline). The animal was killed thirty minutes later by having its throat cut. Necropsy was performed at once, and the kidneys examined both with the naked eye and by means of sections of the fresh tissue (made with a double bladed Valentine knife) studied with a low power lens.

The findings were: 1. The bladder urine was blue (alkaline). 2. A blue color was present in the medulla throughout. This fluid was readily expressed by light pressure and was evidently alkaline urine in the collecting ducts. 3. The cortex was red (acid). The red dye was most concentrated in the cells of the convoluted tubules. 4. No dye reaction was demonstrable in the glomeruli. 5. The outer medullary zone was distinctly reddish (acid). 6. The medullary rays were grossly bluish (alkaline), but a few loops of Henle which could be fairly accurately identified in the fresh sections contained red (acid) cells.

As noted above, the findings in this whole series were uniformly the same in all the normal animals having an alkaline urine. It is to be noted that when the urine is alkaline (p_H less than 10^{-7}) the cells of the convoluted tubules and the outer medullary zone show an acid reaction. The outer medullary zone differs anatomically from the rest of the medulla only by the additional presence of numerous loops of Henle. The medulla contains an alkaline urine, which is readily pressed out, leaving no dye in the cells of the collecting tubules, but the acid dye reaction in the outer medullary zone cannot be so altered. On study of the fresh sections the dye is seen to be intracellular there, but not so in the collecting tubules of the medulla proper. Therefore, it may be concluded that the acid reaction of the outer medullary zone in these animals with an alkaline urine is due to acid cells of the loops of Henle. The findings in the medullary rays confirm this.

The results of similar experiments with normal dogs show essentially a completely reversed picture. Five normal animals were successfully studied, with uniformly consistent results in all the experiments. Two typical protocols of this series follow:—

Experiment KR. 18.—A young male dog, weighing 10 kg., was fed entirely on meat, largely raw, for four days before the experiment. No water was given on the day before the experiment, but 300 c.c. of water were given one hour before starting the experimental procedure. This preliminary procedure was carried out to insure a rather concentrated and strongly acid urine during diuresis.

The animal was anesthetized with ether, and the left external jugular vein exposed. Into this 30 c.c. of 1 per cent. neutral red in distilled water (0.3 gm. of dye) were slowly injected. The abdomen was then opened and the right kidney exposed to the air. The kidneys were removed ten minutes after the end of the injection, after bleeding the animal to death.

The findings were: 1. The bowels and kidneys showed considerable red color externally. 2. The bladder urine contained a little dye, purplish red (acid). The bladder was full. 3. The renal medulla, seen in surfaces made by cutting, contained purplish red (acid) urine in the tubules. This color was most intense at the lower border of the outer medullary zone. The cells of the collecting tubules were white after expressing the urine. 4. In the cortex the reaction was everywhere yellow (alkaline), both to the naked eye and microscopically in the fresh tissue sections. The convoluted tubules were yellow (alkaline) in reaction throughout. 5. The medullary rays contained some red (acid) urine, but not in all the tubules. This red color was confined to the lumina of the tubules there. 6. The outer medullary zone was not clearly demarcated.

Conclusion: With an acid urine, the cortical reaction was everywhere alkaline.

Experiment KR. 51.—A normal female dog, weighing 8 kg., was anesthetized with ether. The left external jugular vein was then exposed, and 40 c.c. of a saturated solution of azolitmin in distilled water was injected intravenously with no appreciable reaction. Ten minutes later the carotid artery was cut, and the dog bled to death. While bleeding the abdomen was opened and the kidneys removed immediately on the death of the dog.

The findings were: 1. The bladder urine was reddish (acid). 2. The urine in the renal pelvis was red (acid). 3. The urine in the medullary collecting tubules was red (acid) on both sides. 4. The cortexes of both kidneys were

bluish (alkaline), but in some places the intensity of the blue was greater than in others. 5. The outer medullary zone in both kidneys was decidedly bluish (alkaline). In sections made with a Valentine knife it was seen that this blue dye was present only in certain tubules, while others which were directly continuous with the purely collecting tubules of the lower medulla contained no dye in their cells. Therefore the tubules with the alkaline cells must be Henle's loops. 6. One lobe, or pyramid with the cortex above it, showed a reversed reaction: bluish (alkaline) urine in the papilla, reddish (acid) cortex—convoluted tubules—and reddish (acid) outer medullary zone.

Conclusions: 1. This experiment confirms the normal findings in the dog that with an acid urine the convoluted tubule and loops of Henle cells are alkaline, with azolitmin in place of neutral red. 2. One or more lobes of a kidney may be secreting an alkaline urine, while the rest is secreting an acid urine, with an excess of the acid form, making the mixed result (bladder or ureteral urine) acid.

The observation that one or more lobes of a kidney may be secreting a urine of the opposite reaction was also noted in two other experiments with dogs (KR.38 and KR.41), in both of which sodium alizarinate was used. This is of considerable interest, as heretofore it has been largely assumed that even if the whole kidney does not secrete uniformly in the quantitative sense, it at least does so qualitatively. These observations show that that is not the case. The absence of this phenomenon in the rabbit is undoubtedly due to the fact that this animal has a unilobar kidney.

Two other phenomena were studied in normal animals. One was the intensification of the normal alkaline reaction of the urine in the rabbit by the administration of sodium bicarbonate, and the other the alkalinization of the dog's urine by the same means. Protocols of two such experiments follow:

Experiment KR. 20.—Twenty cubic centimeters of 10 per cent. sodium bicarbonate was put into the stomach of a young male rabbit, weighing 1,200 gm., by catheter. After fifteen minutes 10 c.c. of 1 per cent. neutral red were injected into a marginal ear vein, with no apparent toxic effect. The animal was killed ten minutes later by having its throat cut, and necropsy was performed immediately.

The findings were: 1. The bladder urine was yellow (strongly alkaline). 2. The medullae were also yellow (strongly alkaline), due to the urine in the collecting tubules, which was readily expressed. 3. The cortexes contained much purplish red (acid) dye. With the microscope its was seen that this color was in the convoluted tubules, and that the bluish (strongly acid) tint was decided. 4. The medullary rays in the cortex were yellow (alkaline), in contrast to the bluish red (strongly acid) reaction in the convoluted tubules. This alkaline reaction was in the lumina of the collecting tubules. The acid reaction of the convoluted tubules was more marked in this experiment than in the normal animals who had not received alkali.

Experiment KR. 60.—A young male terrier, weighing 6.5 kg., was given 18 gm. of sodium bicarbonate in 350 c.c. of tap water by a stomach tube. The animal did not vomit. One hour later the dog was anesthetized with ether, the right femoral canal opened and the femoral vein exposed. This was cannulated, and 250 c.c. of 0.5 per cent. neutral red in physiologic sodium chlorid were introduced into the circulation, without an appreciable toxic effect. Ten minutes later the abdomen was opened, and the dog was killed by the cutting of the aorta. The kidneys were removed at once and examined.

The findings were: 1. The bladder urine was cloudy and orange (alkaline). 2. Both kidneys were small, the capsules stripped readily, leaving smooth glistening surfaces. Surfaces made by cutting showed no gross anatomic changes. 3. In the medullae the tubules contained an orange red (alkaline) urine, which was easily squeezed out. After pressing this out, the medullary tissue was white. 4. The outer medullary zones were conspicuous, sharply demarcated and raised on cut surface. They were purplish red (acid). 5. The cortexes were also purplish red (acid), and most of this color was in the labyrinthian portion. In sections made with a Valentine knife it was seen that the dye was in the cells of the convoluted tubules. The intensity of the color was greatest in the cortex.

Conclusions: When the reaction of the urine in the dog is changed from the normal acid to an alkaline one, the reaction of the secreting cells is changed from alkaline to acid.

Thus it is demonstrated that exaggeration of the intensity of the normal alkaline reaction of the rabbit's urine causes an increased intensity of the acid content of the secreting cells. In the normal animal it was invariably found that the reaction of the urine was the opposite to that of the cells of the convoluted tubules and Henle's loops. This relationship is retained even though the reaction of the urine is reversed by the administration of alkali. It is of considerable clinical significance that the renal cells are acid when secreting an alkaline urine.

After several unsuccessful attempts to obtain a normal animal secreting a neutral urine (p_H 10^{-7}), one was obtained. The results of this experiment are recorded in Experiment KR.66.

Experiment KR. 66.—A small male dog, weighing 8 kg., was given a meat free diet for two days and then very salty food containing also some sodium bicarbonate. Just before the experiment the dog was allowed to drink a large amount of water. One hour later the animal was anesthetized with ether, the left external jugular vein exposed and 50 c.c. of a saturated solution of azolitmin in distilled water injected intravenously. Ten minutes later the animal was killed by cutting the abdominal aorta. The kidneys were removed at once and examined.

The findings were: 1. The bladder urine was violet (neutral). 2. Both kidneys were grossly normal throughout. 3. Both medullae contained purplish red or violet (neutral) urine, which could be readily expressed with light pressure. 4. The outer medullary zones were sharply defined in both kidneys, and were dark, purplish red (neutral). This part of the kidney contained more dye than any other. 5. The cortexes were purplish red (neutral) throughout, and the dye was almost all, if not all, in the cells of the convoluted tubules.

Conclusions: With a neutral urine (p_H 10^{-7}) in the dog, the reaction of the kidney secreting cells is also neutral.

The experiments reported above are typical examples of the results obtained with about twenty-five normal animals. The findings were repeatedly confirmed by using all three of the indicator dyes. In no instance were results obtained which deviated from the general picture. It may be safely concluded that the secreting cells of the normal kidney have the opposite reaction to the urine; when the latter is acid, the cells of the convoluted tubules and Henle's loops are alkaline, and when the urine is alkaline the reversed reaction obtains in the cells. Further-

more, exaggeration of the alkalinity of the urine leads to an increase in the intracellular acidity. The whole kidney does not function identically at a given time in the qualitative sense, but one part may be secreting an alkaline urine while the rest forms an acid one. Lastly, when the urine is just neutral, the cells are also neutral.

The hydrogen-ion concentrations of cells and urine were simultaneously studied in eighteen animals with experimentally induced nephritis. Seven rabbits were studied, in six of which an acute tubular toxic nephritis was produced by the subcutaneous injection of mercuric chlorid or sodium potassium tartrate [12] twenty-four hours before the injection of the indicators (Experiments KR.40,42,45,46,48 and 49). In these experiments each of the three dyes was used, and further control was obtained by the use of the same dye for each of the two forms of toxic nephritis. The results were uniform in all of the experiments, and a protocol of one will suffice as an example.

Experiment KR. 48.—A large female albino rabbit, weighing 1,800 mg., on July 15, 1923, at 4 p. m., was given 2 gm. of sodium potassium tartrate (Rochelle salts), injected subcutaneously into the back. The animal was returned to the cage. On July 16, at 4:30 p. m., the animal was lying quietly in the cage, apparently quite toxic. There was some diarrhea. Twelve cubic centimeters of 1 per cent. neutral red in distilled water was injected into the marginal ear vein, with no reaction. The animal was killed twenty minutes later by decapitation.

The findings were: 1. The bladder urine was bluish red (acid). 2. The two kidneys were alike, swollen, pale and opaque, bulging when the capsule was stripped. 3. The medullary pyramids contained bluish red (acid) urine, which could be easily pressed out of the ducts. 4. The outer medullary zones were distinctly orange to yellow (alkaline). With the microscope the dye was here seen in the cells of Henle's loops. 5. The cortexes were deep purplish red throughout (acid). Fresh sections localized the reaction here as being in the cells of the convoluted tubules. 6. Formaldehyd fixed frozen sections stained with hematoxylin and eosin showed an acute degenerative process in the convoluted tubules, with no apparent change in the glomeruli or loops of Henle.

The fact that the loops of Henle retained their normal relationship of the opposite reaction to that of the urine is of interest. The histologic study and previous observations support the impression that these cells are not severely damaged by the intoxication. It has long been known that the tartrates injure primarily the convoluted tubules [13]. One rabbit with spontaneous nephritis was encountered (KR.14.) in which the entire kidneys, urine and cells alike, were acid in reaction. This animal had distemper, some ascites and diarrhea. Paraffin sections of the kidney revealed a thinned cortex, with distended tubules lined with flattened cells and some acute increase in the connective tissue and round cells. One large area in the cortex, extending from the renal

12. Underhill, Wells and Goldschmidt: J. Exper. Med. **18**:317, 1923. Stieglitz: Am. J. Anat. **29**:33, 1921.

13. Stieglitz: Am. J. Anat. **29**:33, 1921.

capsule to the arcuate arteries was almost entirely replaced by round cells. In dogs similar studies were undertaken, and in five animals (KR.54,62,63,64, and 65) an acute toxic tubular nephritis was induced. The results of these experiments are essentially similar to those observed in the rabbits. A single typical protocol will suffice.

Experiment KR. 63.—A male dog, weighing 9 kg., on Aug. 21, 1923, was placed in a metabolism cage with plenty of water. On August 22, the urine was acid. No albumin, no casts or sugar were present. The specific gravity was 1.034. The animal was given a subcutaneous injection of 0.1 gm. of mercuric chlorid.

On August 23, the dog was very quiet and listless. Urinalysis revealed: albumin, a few casts, acid, no sugar. The animal was anesthetized with ether, and 150 c.c. of 1 per cent. neutral red in distilled water were given into the right femoral vein by gravity through the cannula. Five minutes after the end of the injection the abdomen was opened, and the animal was killed by bleeding from the aorta. The kidneys were removed at once and examined.

The findings were: 1. The bladder was distended with acid urine, containing considerable albumin. 2. The two kidneys were alike—very soft, moist and opaque. 3. The medullae contained purplish red (acid) urine which was easily expressed from the ducts by light pressure. 4. The outer medullary zones were clearly demarcated and distinctly bluish red (acid). This color could not be pressed out. 5. The cortexes were purplish red (acid) throughout, the color being most concentrated in the labyrinthian portion. 6. The medullary rays contained little dye. 7. Frozen sections stained with hematoxylin and eosin showed an acute tubular degeneration involving chiefly the convoluted tubules. The glomeruli appeared to be unaltered.

Conclusions: In acute toxic (mercuric chlorid) nephritis in the dog, as in the rabbit, the urine, loops of Henle and convoluted tubules are all acid.

These results confirmed the findings in nephritic rabbits. Two dogs (KR.43 and KR.50) with a long standing chronic unilateral nephritis were similarly studied, the unaltered kidney acting as the normal control. The findings in these experiments are essentially similar to those in the acute nephritis.

Experiment KR. 45.—A male dog, weighing 10 kg., on May 26, 1923, was anesthetized with ether, and under careful aseptic conditions the right kidney was exposed through a posterior nephrotomy incision; a "bull dog" clamp was placed on the right renal artery and left on for fifteen minutes. After its removal the kidney was slipped back into place and the wound closed in layers. The anesthesia was carried throughout without difficulty, and the dog recovered rapidly. On May 27, the dog was recovering well. Urinalysis showed: blood + + + +, albumin + + +. From May 29 to June 19, the dog continued in excellent condition, the wound closing completely. The urine continued to show albumin and casts. Hematuria disappeared about June 1. On July 6, the weight was 8 kg. There have been no manifestations of intoxication or edema. On July 8, urinalysis revealed: albumin +; one or two casts; acid; specific gravity, 1.023. On July 9, the dog was anesthetized with ether, and 50 c.c. of a saturated solution of sodium alizarinate were injected intravenously. After ten minutes the abdomen was opened and the aorta cut. The kidneys were promptly removed and examined.

The findings were: 1. The right (injured or nephritic) kidney was firmly bound down by fibrous adhesions, which were especially marked on the posterior surface, at the pedicle and upper pole, the latter being firmly adherent to the hepatic capsule. The renal capsule was stripped with difficulty, leaving a rough,

granular, rather dry yellow surface. The cortex was moderately narrowed and quite firm. The dye reaction was the same throughout all parts of the kidney, yellow or acid. The urine in the collecting tubules of the medulla and in the renal pelvis was bright orange yellow (acid). The cortex was also yellow (acid), and in sections made with a Valentine knife, examination with a low power lens revealed that the dye here was chiefly in the cells of the convoluted tubules. The outer medullary zone was also yellow (acid) in reaction. Blocks of tissue were fixed in 10 per cent. formaldehyd solution.

2. The left (uninjured or control) kidney was readily removed from the surrounding fat. The renal capsule stripped easily, leaving a smooth glistening surface. The kidney was cut through in many places and showed yellow to orange (acid) urine in the pelvis and collecting ducts of the medulla. The outer medullary zone contained many vertical purple (alkaline) markings, between which were whitish yellow tissue. With the microscope the purplish (alkaline) tubules appear to be loops of Henle. In the cortex the dye was most concentrated in the outer zone, where it was purple (alkaline), and in the cells of the convoluted tubules (microscopic examination of fresh sections). No gross pathologic condition was seen. Pieces of this kidney also were fixed in 10 per cent. formaldehyd solution.

3. The bladder urine was acid, and contained albumin and casts. 4. No other gross pathologic findings were detected by a complete necropsy. 5. Histologic findings of the fixed tissue, stained with hematoxylin and eosin showed: Right or damaged kidney: The cortex was very thin; many tubules were dilated; there were some connective tissue scars, but no necrotic tissue was seen. The cells appeared to be edematous, staining poorly with eosin. Many of the tubule cells were desquamated. The left or control kidney was normal.

Conclusions: In a kidney damaged forty-four days before by a transient asphyxia, the hydrogen-ion concentration of the cells and urine are similar to those found in an acute nephritis, the damaged cells and urine both being acid, while in the opposite control kidney of the same animal the reaction of the cells was alkaline in the normal relationship to the acid urine.

The findings in Experiment KR.50, in which the same procedures were carried out, were identical. Several experiments dealing with acute asphyxia of one kidney were carried out (KR.52,53,58,59). The fact that asphyxiated cells become temporarily acid in reaction has long been known, and this was again demonstrated in these experiments. The dogs were anesthetized with ether, the indicator injected intravenously, a renal pedicle exposed and the renal artery clamped for fifteen minutes. After the removal of the clamp the dogs were bled to death and the kidneys examined at once. In all instances the asphyxiated kidney was acid in reaction through the whole of its substance, urine and cells alike, whereas in the opposite normal control kidney the normal reaction pertained, acid urine and alkaline secreting cells. The appearance of both physiologic and anatomic evidence of nephritis as long as forty-four days after a transient fifteen minute asphyxia is of great importance. A rather careful search of the literature revealed no previous mention of such persistent damage. Asphyxia, even though transient, apparently results in serious injury which lasts for a considerable time.

An investigation of the effects of alkaline therapy on nephritic dogs was also undertaken. Three experiments (KR.62,64 and 65) were performed. In one of these (KR.64), not enough alkali (sodium

citrate) was given to alkalinize the urine, and the findings were the same as those for the untreated nephritic animals. In Experiment KR.62, the animal was rendered nephritic with mercuric chlorid and given sodium bicarbonate by stomach tube to alkalinize the urine. Here it was found that the urine was alkaline, the outer medullary zone or loops of Henle acid, and that there was an almost complete absence of dye in the convoluted tubules. The absence of the dye there was probably due to the fact that the severely damaged convoluted tubules were not secreting the dye, throwing the burden on the loops of Henle. Alkalinization of the urine in the normal animal causes the cells to become acid, and, as would be expected, it does not bring the reaction of the damaged cells to the alkaline side.

In Experiment KR.65 we were fortunate enough to just neutralize the urine of a nephritic dog. The protocol of this is reported below.

Experiment KR. 65.—A male dog, weighing 8 kg., on Aug. 23, 1923, was thin and poorly nourished; otherwise he was apparently healthy. Urinalysis revealed: no albumin; no casts; acid; specific gravity, 1.032. An injection of 0.08 gm. of mercuric chlorid in 4 c.c. of distilled water was given subcutaneously. The animal was then returned to the metabolism cage. On August 24, the animal was very listless and quiet, and had a mushy diarrhea. Urinalysis revealed: albumin + +; casts; acid; specific gravity, 1.038. At 1:30 p. m., the dog was given 15 gm. of sodium bicarbonate by stomach tube in 300 c.c. of tap water. Ten or fifteen minutes later some of this was vomited. At 2 p. m., the animal was anesthetized with ether and 200 c.c. of 1 per cent. neutral red in physiologic sodium chlorid introduced through a cannula into the right femoral vein. Five minutes later the animal was killed by cutting the aorta. The kidneys were examined at once.

The findings were: 1. The bladder was almost empty. The urine present was neutral (tested with both neutral red and azolitmin), p_H 10^{-7}. Albumin was present. 2. Both kidneys were very soft and swollen. The cortical markings were not clear. 3. The medullary urine was red, neither orange nor purplish (neutral). 4. The outer medullary zone was clearly demarcated and contained much red (neutral) dye. 5. The cortexes contained less dye; this was distinctly purple (acid) and was found in the degenerated convoluted tubules (fresh sections).

Conclusions: By chance a nephritic kidney was studied which was secreting an exactly neutral urine. The urine and loops of Henle were both neutral as in a normal kidney under similar physiologic conditions, but the more severely damaged convoluted tubules remained acid. The great concentration of the dye in the cells of Henle's loops may be due to an excessively active secretion there, as the convoluted tubules were almost completely destroyed.

CONCLUSIONS

If we sum up the results obtained, and described above by some typical examples, it may be concluded that the following facts are established: When the kidney is secreting an acid urine, the cells of the parenchymatous tubules, both the convoluted tubules, proximal and distal, and the loops of Henle (thick limb) are alkaline in reaction. When the urine is alkaline these same cells are acid. When the alkalinity of the urine is exaggerated, the acid reaction of the cells is

increased, but it is impossible to say from the present studies to what degree. In all the nephritic kidneys studied the damaged cells presented an acid reaction, irrespective of the reaction of the urine.

DISCUSSION

The results recorded above indicate that the cells of the convoluted tubules and loops of Henle are essentially involved in the determination of the hydrogen-ion concentration of the urine. The reaction of the cells of these tubules bears a constant relationship to the reaction of the urine. They are the only renal cells in which the indicator dyes appear, and, as the dyes are secreted into the urine, they probably are passing through the cells. The fact that these cells invariably have the opposite reaction to that of the urine in the normal kidney is of considerable physiologic significance. It indicates that cells secreting an acid product retain temporarily the complementary basic components, making the cell content alkaline in reaction; and vice versa, when the cells eliminate an excess of basic products, they retain complementary acid components. We may imagine, for instance, this separation of base and acid to occur with the aid of the amphoteric proteins (amino-acids) of the cells which may combine with either the acid or the basic component of a hydrolyzed salt, in the form of protein salts. As these salts in turn are hydrolyzable in the way that all salts of weak bases or weak acids are, the reaction of the cell contents would be basic if the retained component is the base in combination with an acid radical of a protein, and the reverse would be true if the retained component is the acid combined with a basic radical of a protein. This conception is in line with the work of Nash and Benedict,[14] who showed that the ammonia of the urine is formed in the kidney.

However, the question whether the convoluted tubules are elements of secretion has not been universally conceded. On the whole, there are two chief schools of thought concerning the mechanism of renal secretion. The one, first presented by Bowman,[15] teaches that the glomeruli secrete water and some salts, and that the convoluted tubules concentrate the urine by the additional *secretion* of salts and nitrogenous products. The other school, founded on the theories of Ludwig[16] and now largely supported by Cushny,[17] maintains that the concentration of the urine is accomplished by the *reabsorption* of water and certain "threshold" bodies by the convoluted tubules. The gist of the situation therefore is: Do the convoluted tubules *secrete* or *reab-*

14. Nash and Benedict: J. Biol. Chem. **48**:463, 1921; ibid. **51**:183, 1922.
15. Bowman: Philos. Trans. **57**:1842.
16. Ludwig: Mechanismus der Harnsecretion, Marburg, 1843.
17. Cushny: The Secretion of Urine, Monographs of Physiology, London, Longmans, Green and Co., 1917.

sorb substances to or from the urine, or do they do both? That secretion does take place by these cells has been proven to be the case for several substances, such as urea [18] and iron.[13] Cushny [17] postulates that the chief source of the sodium hydroxid reabsorbed is from the phosphates,[19] by hydrolysis of sodium phosphate. Richards [20] has recently added supporting data to the theory of reabsorption.

As regards the observations on hydrogen-ion concentrations in the cells and urine, the fact that the cells are of the opposite reaction to that of the urine may be interpreted by either theory. The cells may be alkaline because of a secretion of acid into the urine, or because of the reabsorption of bases, leaving the urine acid. But in the experiments on the rabbit in which the alkalinity of the urine was increased by the administration of sodium bicarbonate (KR.20), the acid reaction of the cells was also exaggerated. In view of the fact that greater alkalinization of the urine by the addition of alkali leaves less acid to be absorbed from the urine by the cells, we are forced to the conclusion that the increased acidity of the cells is not due to reabsorption of acid from the urine. If, on the other hand, the cells are secreting a preponderance of bases from the neutral blood, a greater accumulation of intracellular acid might well occur. Therefore the observations recorded above serve to support the theory that the concentration of the urine and determination of the acid or alkaline reaction thereof is accomplished by secretion by the tubule cells.

In several instances in the nephritic animals studied it was noted that when the convoluted tubules were severely damaged and contained little dye, the loops of Henle were abnormally heavily laden therewith. It may be suggested that the loops of Henle take over the function of secretion when the convoluted tubules are so severely damaged. That this is so is by no means firmly established by these findings, but they strongly suggest such function on the part of Henle's loops.

In the nephritic kidneys it was invariably found that the injured cells were acid in reaction. Fischer [2] discusses the increased hydrogen-ion concentration of injured or asphyxiated tissue at length. He declares that the greatest hydrogen-ion concentration in the urine occurs in acute nephritis, and claims that the p_H of the urine is a valuable aid in making the prognosis of nephritic cases and in determining the condition of the kidneys. He has also shown that in nephritis the acid combining power of the blood is decreased. Araki [21] and Zillessen [22] showed that in asphyxiated tissue there is an accumulation of acid. These observations are entirely in accord with those recorded above.

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18. Oliver: Jour. Exper. Med. **23**:301, 1916.
19. Cushny: Jour. Physiol. **31**:188, 1904.
20. Richards: Am. J. Med. Sc. **163**:1, 1922; Am. J. Physiol. **59**:184, 1922.
21. Araki: Ztschr. f. physiol. Chem. **15**:335 and 546, 1891; ibid. **19**:473, 1894.
22. Zillessen: Ztschr. f. physiol. Chem. **15**:387, 1891.

Fischer [2] maintains that edema and albuminuria are both the result of increased intracellular hydrogen-ion concentration, and that inhibition of secretion is a result of altered hydration capacity of the tissue colloids, similarly induced. In this connection it is important to study the effects of alkali therapy. A normal kidney secreting an alkaline urine has acid cells, therefore alkalinization of a nephritic person's urine should certainly not alkalinize the cells. In fact, the more alkaline the urine becomes, the more acid are the cells, and this might well increase the damage, especially as the injured cells are already acid. Therefore it may be concluded that excessive alkaline therapy in nephritis is to be avoided, and that the optimum condition to be obtained is *neutralization* of the urine. If the urine is neutral, normal secreting cells will also be neutral, thus maintaining a reaction best suited for the repair and recovery of the injured cells. Clinical observations confirm these conclusions; over alkalinization not infrequently leads to an acute exacerbation of symptoms. Recently Brown and his coworkers [23] reported evidences of toxic nephritis associated with the alkalosis of duodenal obstruction.[24]

SUMMARY AND CONCLUSIONS

1. When acid urine is being secreted the cells of the convoluted tubules and loops of Henle are alkaline in reaction (using $p_H 10^{-7}$ as the neutral point).

2. When alkaline urine is being secreted, these cells are acid.

3. When neutral ($p_H 10^{-7}$) urine is secreted, the cells are neutral also.

4. Increase in the alkalinity of the urine leads to increased acidity of the cells.

5. In the dog, one or more lobes of a kidney may be secreting an alkaline, the rest an acid, urine simultaneously.

6. Alteration of the reaction of the urine causes a similar, but opposite, change in the reaction of the cells.

7. The reaction of the urine is controlled by the convoluted tubules and loops of Henle.

8. The reaction of the urine is determined by *secretion* of either an excess of acid or alkali by these cells.

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23. Brown, G. E.; Eusterman, G. B.; Hartman, H. R., and Rowntree, L. G.: Toxic Nephritis in Pyloric and Duodenal Obstruction: Renal Insufficiency Complicating Gastric Tetany, Arch. Int. Med. **32**:425 (Sept.) 1923.

24. Since the paper was sent to the publishers, H. F. Shattuck, E. L. Rohdenburg and Lela E. Booher have reported similar observations (J. A. M. A. **82**:200 [Jan. 19] 1924).

9. In nephritic kidneys the injured cells are acid in reaction, as is the urine, the normal relationship thus being destroyed.

10. Alkalinization of the urine in nephritic animals does not reverse the acid reaction of the cells.

11. Alkali therapy in nephritis must not be carried to a point of alkalinization of the urine, as that tends to increase the intracellular acidity. Neutralization of the urine, however, is desirable.

AN IMPROVED AIR VALVE FOR APPARATUS USED IN BASAL METABOLIC WORK*

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A special series of experiments[1] to determine the metabolic rate (this is done by the collection and analysis of expired air) of subjects exposed to varying temperatures and humidities was conducted under the supervision of Dr. R. R. Sayers and Dr. W. J. McConnell as part of a cooperative study of the physiologic effects of atmospheric conditions being made by the Bureau of Mines and the American Society of Heating and Ventilating Engineers. In this work a number of different types of valves were experimented with in order to select the one best suited. The deciding factor in selecting a valve for use in basal metabolic work rests with its ability to prevent any small amount of air from escaping around the edges of the valve when closed, which may be designated as "slip leakage."

Several types of valves are available which, though satisfactory for use in certain breathing apparatus, could not be used in these experiments. The so-called "mica-disk" valves must be kept in a horizontal position in order to function properly; and it is impractical to do this with the subject lying down. There is a small amount of slip leakage with such a valve even when held in the horizontal position, especially in slow and shallow breathing. This leakage has been eliminated by a few manufacturers who have inserted a small spring behind each disk, thus causing it to close more quickly and seat more firmly. Sometimes these disks have small ridges that permit leakage. Also, the clicking sound in closing annoys some people. Other types of valves are those used with the mask type of oxygen apparatus and those with the mouthpiece type. In the mask type there is always the possibility of a leak around the mask, and the increased dead air space gives rise to erroneous results; while in the mouthpiece type it is impossible to have leakage, and the dead air space is decreased to a minimum.

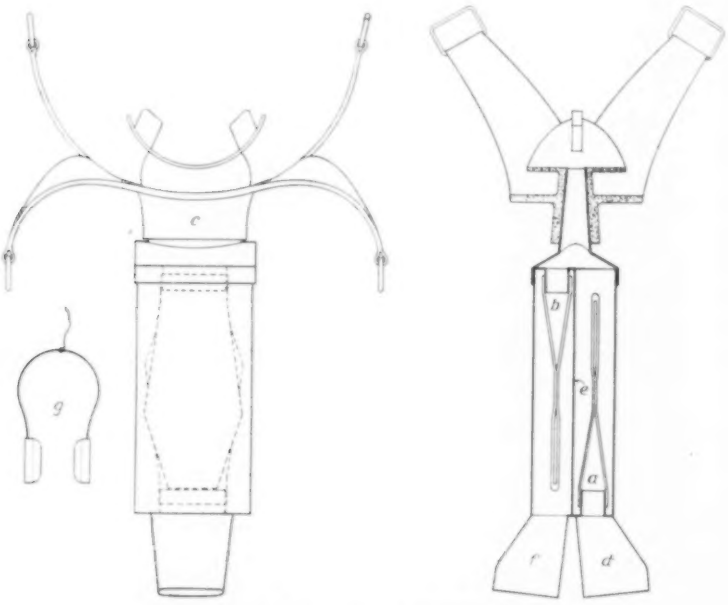
The use of the water valve is impracticable in basal metabolic work, because the difference in pressure causes a resistance to breathing, which is objectionable.

I have developed an improved type of valve and used it successfully in the collection of samples for basal metabolic work at the Pittsburgh

* Published by permission of the Director, Bureau of Mines, Department of the Interior.

1. Results of these investigations are shortly to be published.

Experiment Station. This improved valve, worked out by the Bureau, is a modification of the Douglas [2] valve, which, with other valves similarly constructed, has been used in apparatus for basal metabolic work. Figure 1 shows the details of the valve used by the Bureau. *a* is the inhalation valve, and *b* is the exhalation valve; *c* is the rubber mouth piece; *d*, a pipe for rubber tube connection on the inhalation side; *e*, a tin partition between the two valves; *f*, a pipe for the rubber tube connection to the spirometer; and *g*, the nose-clip.



Double action rubber butterfly valve.

The two butterfly valves (the rubber valves used for exhalation in the army type of gas mask) are placed parallel to each other but in opposite directions in a tin air-tight container 3¾ by 1¾ by 1¼ inches, and are separated by the tin partition. The valves are held at the base ends in such a manner that when not in use they are closed. The rubber mouth piece is coated with shellac, and is fastened securely to the container. Two pipes ⅞ inch in diameter connect the container with the apparatus. These, because of their size, eliminate most of the resistance in the rubber tube connections.

2. Douglas, C. G.: A Method for Determining the Total Exchange in Man, J. Physiol., March 18, 1911, p. 17.

The valve described herein is simple in construction and inexpensive, yet it can be operated in any position without incurring the objectionable features of other types. It has been successfully used by the Bureau of Mines, and should be particularly well adapted to collecting samples of air for basal metabolic or allied work.

AURICULAR FIBRILLATION IN GOITER

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Recently Schoonmaker and Webb [1] reported a case of auricular fibrillation in a toxic adenoma of the thyroid. Because of the great improvement noted in all symptoms in this case and the rarity of this condition among our patients with goiter we thought it worth while to investigate the literature on this subject.

In looking through the literature we find that as yet not many cases have been reported in detail, and that as a rule there are only incidental references to cases of goiter in descriptions of various cardiac conditions. However, that auricular fibrillation is not rare in goiter is shown by Willius [2] who stated that at the Mayo clinic 7 per cent. of patients with exophthalmic goiter and 9 per cent. with hyperactive adenoma have auricular fibrillation on admission, and that these figures were doubled while the patients were under observation. Willius and Boothby [3] in a more recent paper, gave figures of 22 per cent. in exophthalmic goiter and 24 per cent. in adenoma with hyperthyroidism. On the other hand, in their book on the thyroid gland, Crile and his associates [4] described one case in some detail. Apparently, at the Cleveland clinic this condition was not found so frequently. Hamilton,[5] in a series of 200 cases of goiter at a Boston clinic found eighteen cases of fibrillation among hyperthyroid cases, while Hamilton and Lahey [6] stated that 10 per cent. of patients with goiter have an absolutely irregular heart either as an established or recurrent condition.

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1. Schoonmaker, H., and Webb, C. W.: Report of a Case of Goitre (Adenomatus Type) Complicated by Auricular Fibrillation, Clifton M. Bull. **8**:2, 1922.

2. Willius, F. A.: The Heart in Thyroid Disease, Ann. Clin. Med. **1**:269, 1923.

3. Willius, F. A., and Boothby, W. M.: The Heart in Exophthalmic Goitre and Adenoma with Hyperthyroidism, Med. Clin. N. Am. **7**:189, 1923; Heart in Exophthalmic Goitre and in Adenomatous Goitre with Hyperthyroidism, J. A. M. A. **80**:1725 (June 9) 1923.

4. Crile and Associates: The Thyroid Gland, Philadelphia, W. B. Saunders Company, 1922.

5. Hamilton, B. E.: Clinical Notes on Hearts in Hyperthyroidism, Bost. M. & S. J. **86**:216, 1922.

6. Hamilton, B. E., and Lahey, F. H.: Differentiation of Hyperthyroidism and of Healt Disease from Neurasthenic State, J. A. M. A. **78**:1793 (June 10) 1922.

REPORT OF CASES

CASE 1.—*History.*—A woman, aged 46, was admitted to the hospital on Jan. 30, 1922, complaining of rapid and irregular heart, nervousness, insomnia, loss of weight, small physical endurance and recurrent attacks of abdominal cramp, nausea and vomiting. Her father had diabetes at the age of 76, and her mother died of pulmonary tuberculosis at the age of 33; otherwise the family history was negative. She had had some childhood diseases, typhoid fever, tonsillitis at the age of 40 and once previously. She had two normal healthy children.

Her present illness began ten years before (1912). In 1913, she had had an Alexander operation, followed by cessation of the abdominal attacks, which, however, began again in 1916, and necessitated two months' rest in bed. Six months later she had a recurrence of the attack followed by three months' rest in bed and dietary treatment. She had had many similar attacks, although they had been less severe since that time. A goiter was first observed in 1913. Toxic symptoms were clearly evident in 1916. It is not clear when auricular fibrillation developed, but probably as long as six months before admission to the hospital.

Examination.—On admission the patient could exercise only about 60 per cent. of her normal capacity, and her heart was rapid and irregular. It never was definitely incompetent. Her weight was 115 pounds (52.2 kg.), about 10 pounds (4.5 kg.) below her normal weight. Her expression was anxious, and she had large infected tonsils. Both lobes of the thyroid were enlarged and irregular, the left more than the right. There was a soft systolic murmur at the apex of the heart, which was somewhat enlarged and absolutely arrhythmic. The heart rate was 120 with a pulse deficit of 40. There were tremor of the fingers and rigidity of the abdomen. The laboratory findings were: negative urine and Wassermann tests, slight secondary anemia and a basal metabolism of 119 per cent.

Fluoroscopy of the chest revealed: trachea slightly displaced toward the right and somewhat compressed above the level of the manubrium. The upper mediastinum showed a shadow suggesting an enlarged thyroid projecting down a very short distance in the upper mediastinum. The aorta was normal. The heart was moderately enlarged both to the right and left, with marked prominence of the auricular curve suggesting mitral disease. The action was rapid, tumultuous and decidedly irregular. The lungs showed increased fibrosis extending outward from both hilums with increase in the hilum shadows. The left apex had a suspicious appearance, but this appearance may have been caused by the substernal thyroid. The diaphragm was negative.

Several cardiograms were made. Before operation several were alike in showing no "P" deflection and the absence of ventricular rhythm as is characteristic of auricular fibrillation.

Treatment and Course.—The first thing attempted was to regulate the heart by rest in bed, the placing of an ice bag on the precordium, and the administration of tincture of digitalis, 15 minims (0.92 c.c.) every four hours. The gastric symptoms were believed to be a part of the symptoms of toxic goiter. After four days the heart rate was quite constant and varied from 90 to 100 with no pulse deficit. It was then decided that no essential heart lesion existed and that the arrhythmia was toxic in origin. On February 17, thyroidectomy was performed. The left lobe was larger than the right, but both lobes were considerably enlarged, with several adenomas in each lobe. Practically all of the left and all but a small portion of the right lobe were removed. Convalescence occurred without complications. Three days after operation the heart became regular and has remained so. The maximum rate after cessation of fibrillation was 80, and the rhythm was normal.

A cardiogram was made five weeks after operation (March 23) which was normal, except for a flat or negative "T" deflection. This was thought to be

evidence of remaining thyroid toxicosis. An electrocardiogram two months later (June 20) was normal.

The patient left the hospital on April 7, much improved in weight and strength. There were no murmurs in the heart, rhythm was normal, and the sounds were of good quality. Six weeks later the patient appeared normal; she had gained 25 pounds (11.3 kg.) and had no heart nor abdominal symptoms.

Microscopic Examination.—The microscopic sections showed some increase of connective tissue with hyalin changes and calcium deposits. Some of these areas showed rather large vascular spaces. The follicles were lined with low columnar cells. A few were dilated, some with colloid; others were empty. The section looked somewhat like a fetal adenoma with some angiomatous areas.

Diagnosis: adenoma, microscopically only slightly active.

CASE 2.—*History.*—A man, aged 49, entered the hospital on June 13, 1922, complaining of a rapid heart and loss of weight. He had had some of the childhood diseases, and influenza in 1920; there had been some flatulence, especially since 1917 after extraction of several teeth. His present illness began a year before with attacks of palpitation. He had had several attacks since then, the last one about two weeks before. He had lost about 30 pounds (13.6 kg.) in weight in the past six months.

Examination.—Physical examination revealed small tonsils and a small nodular mass in the region of the left lobe of the thyroid. The heart was enlarged, rapid and absolutely arrhythmic, the apex rate 120, the pulse rate 90. The patient had a slight fine tremor of the hands.

Fluoroscopic examination showed the trachea displaced to the left with a shadow extending into the left upper mediastinum. The heart was slightly enlarged and rapid, with diminished force. Laboratory tests revealed a negative blood Wassermann test, a faint trace of albumin in several preoperative specimens of urine, a phenolsulphonephthalein test of 57.2 per cent. in two hours, a normal blood count and a basal metabolism of 126 per cent. The electrocardiogram showed an absent "P" wave and arrhythmic ventricular contractions on June 15. He was given 15 minims of digitalis three times a day, and on the nineteenth there was no pulse deficit. On the twenty-first, a cardiogram still showed auricular fibrillation.

Treatment and Course.—Thyroidectomy was performed on June 22, most of the enlarged left lobe being removed. A good operative recovery was made. The specimen grossly was an adenoma with a small cyst. Sections showed areas of closely crowded small follicles with no, or very little, colloid, lined with tall granular cells; others showed hyalinized connective tissue areas and areas with loose fibrous connective tissue with many vascular areas, diagnosis: Adenoma.

It is not quite clear from the history when the fibrillation ceased, but apparently very soon after operation. A cardiogram on July 7 was normal, except for a slight negative deflection of the "T" wave. On August 15, a note stated that the heart condition was excellent and that the patient had gained weight. In October, he was still progressing favorably.

CASE 3.—*History.*—A woman, aged 51, came to the hospital complaining of diarrhea and shortness of breath. Her past history was negative, except for frequent attacks of diarrhea and a history of colitis ten years before, with which she was troubled for three or four years, and for which considerable silver nitrate was used in irrigations and in tablet form. There was a history of an irregular heart and shortness of breath one year before. Her family history was negative. Her present illness began some time in August, 1923, when she became conscious of palpitation and a rapid heart and had diarrhea. The previous winter she had been well and able to exercise strenuously. With her rapid heart, in August she became short of breath. This became so bad that in September she was put to bed and given digitalis, which resulted in so much improvement that she returned to her position as teacher. The diarrhea began

again, her ankles began to swell, she was short of breath, and her heart became irregular.

Examination.—On entrance to the hospital on October 7, physical examination revealed a nervous woman with marked exophthalmos. There was a definite bluish discoloration of the skin, more marked over the exposed surfaces. The skin was warm and moist, and the neck showed rather diffuse irregular enlargement over the thyroid region. The lungs were clear except for moist marginal rāles. The heart action was tumultuous, irregular in force and rhythm, the rate 160 and the dulness increased transversely. The pulse rate was 120, with a deficit of 40. Abdominal examination was negative. There was some edema of the lower extremities, increased reflexes and marked tremor of the hands.

A fluoroscopic chest examination showed an irregular, enlarged heart, some cloudy lines running from the mediastinum and a high but movable right diaphragm. Laboratory tests revealed a negative Wassermann test and a trace of albumin in the urine. On October 10, the basal metabolism rate was 134 per cent., and a week later it was 126 per cent. Diagnosis then was exophthalmic goiter, auricular fibrillation and argyria.

Treatment and Course.—In her progress it was noted that on rest in bed and administration of massive doses of digitalis her heart became slower and more regular, but the pulse by the end of the week, although there was less pulse deficit, was still somewhat irregular at a rate of from 80 to 110.

The patient was operated on, October 23. The specimen obtained showed definite exophthalmic goiter, except in one area in which the follicles were closely crowded, small, almost cordlike, with tall cells. In many areas the tall lining cells showed marked frayed free surfaces.

The day following operation the patient became restless, was semiconscious, had a rapid, weak pulse and rapid respirations with suppression of urine. She seemed to improve somewhat on normal saline given intravenously, but became worse in a short time. She was then given 5 per cent. of glucose intravenously, which did not revive her from unconsciousness. The patient died that night.

Necropsy.—This showed some broncho-pneumonia in the lower right lobe, a normal heart and fairly normal kidneys, except grossly very dark medullary pyramids. These and the skin sections showed a large amount of silver pigment.

Comment.—This patient apparently had had one attack of auricular fibrillation one year before. The present attack of fibrillation began two months before entrance to the hospital but had been treated with digitalis, and she had improved enough to allow her to begin teaching school. Shortness of breath, irregular heart and diarrhea became so severe about one month before that she was put to bed and finally sent to the hospital. It is rather indefinite as to how long she had had goiter, and the exophthalmos, and a question whether colitis or diarrhea ten years before was not a part of the toxic goiter symptoms. It seems probable that the *diarrhea* present when she entered the hospital was due to the hyperthyroidism. Although she had apparently had one attack of auricular fibrillation, the last attack had become constant.

SUMMARY OF CASES

In the patients with goiter here, then, we have had two women and one man, between 46 and 51 years of age. Two had adenoma, one exophthalmic goiter; one a paroxysmal, the other two, established fibrillation. The heart condition improved in all following the administration of digitalis—two receiving small doses, the last (exophthalmic) massive doses. The first two recovered completely from hyperthyroidism and the heart condition, while one died following operation.

REVIEW OF THE LITERATURE

As has been demonstrated many times in various clinics, the heart condition can and does clear up with complete recovery of the patient. In a rather extended search of the older literature, we find that conditions as least similar to auricular fibrillation, if not true auricular fibrillation, were noted early. Germain Sée,[7] in 1878 stated that rapid hearts in exophthalmic goiter are frequent, and he noted especially that arrhythmia had been overlooked by many. "Un autre phenomenè qui accompagne les palpitations et qui a échappé a l'observation de la plupart des auteurs est l'arrythmie" (p. 169). He believed this to be an important sign in goiter, that it often meant a valvular lesion, but also that it might indicate only functional disturbances. He noted an irregular interval between contractions, unequal force, and that the pulse rate (radial) was often slower than the heart rate; points which all prove, as well as can be done without a cardiogram, that he was dealing with a condition we now call auricular fibrillation.

The cases considered as auricular fibrillation are given in the table. The first one was reported by Griffith,[8] who discussed the pulse rate and tracing, tumultuous heart action and low tension pulse. One of his patients, a woman, aged 35, had tumultuous heart action that improved markedly after administration of iron and digitalis. Whether this particular case was one of fibrillation is not clear, but we believe the two with irregular pulse tracings may be so considered.

Another case also not definitely one of auricular fibrillation was described by Fox.[9] This occurred in a woman, aged 49, with attacks of rapid, irregular heart action lasting about a day. Gerhardt[10] described a case of toxic goiter with a pulse of 100 or more and attacks in which the rate was from 120 to 200, definitely irregular and hardly palpable.

Marie[11] examined some patients particularly for heart irregularity, and found a normal regular pulse tracing. Kocher,[12] and Murray,[13] in discussing cases of goiter, mentioned that some were found accom-

7. Sée, Germain: Symptomes de la maladie de Basedow's, La France med. **25**:689, 1878.

8. Griffith, A. Hill: Grave's Disease. Analyses of Cases from Cliniques of Drs. Little and Glascott, Tr. Ophthal. Soc. of United Kingdom **6**:60, 1886.

9. Fox, H.: Brit. M. J. **2**:1184, 1890.

10. Gerhardt, C.: Ueber krankhafte Pulsationen bei Schlussunfähigkeit der Aortenklappen und bei Basedow'scher Krankheit, Charité Ann. **18**:243, 1891.

11. Marie, P.: Contribution a l'étude et au diagnostic des formes frustes de la maladie de Basedow, These, Paris, 1893.

12. Kocher, A.: Ueber morbus Basedowii, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **9**:1, 1902.

13. Murray, G. R.: Exophthalmic Goitre and Its Treatment, Brit. M. J. **2**: 1245, 1905.

Cases of Auricular Fibrillation Reported in the Literature

Author	Year	Sex	Age	Pulse	Heart	Type of Fibrillation and Time	Type of Goiter	Treatment	Result
Griffith...	1886	F.	35	133	Irregular, tumultuous	.....	Exophthalmic	Iron and digitalis	20 months marked improvement; 3 years eyes well
Fox...	1890	F.	49	Rapid	Irregular	Transient, 8 months	.....	.....	.....
Gerhardt.	1891	F.	32	120-200	.....	Transient	Exophthalmic	Strophanthus, "no good"	Improved
Mosse	1907	F.	68	Irregular	Palpitation, irregular	Persistent, several years	Exophthalmic	.....	.....
Sattler	1909	F.	28	200	Palpitation, very irregular	Attacks, weeks	Exophthalmic	Bed rest, sedatives	Improved, no attacks for two years
Hösslin	1909	F.	..	240, irregular	Palpitation, irregular	Attacks, 5 years	Exophthalmic	Operation	Recovered
Bamberger	1910	M.	34	120-180, irregular	Tachycardia, irregular	Attacks, 6 years	Exophthalmic	Digitalis, ligation, then operation	Still frequent attacks
		F.	41	180-200, irregular	Tachycardia, irregular	Attacks, 6 weeks	Exophthalmic	.....	Still fibrillating
		F.	56	170-180, irregular	Palpitation, decompensated	Attacks, 8 months	Nodular goiter (adenoma?)	.....	Attacks continued
Fahrenkamp	1914	..	..	Rapid, irregular	Rapid auricles, irregular ventricles	Intermittent	Exophthalmic	.....	.....
Krumbhaar	1918	F.	..	.....	Fibrillation, mitral stenosis	Transient, 18 months	Toxic adenoma	Operation (?)	Normal heart
White and Aub	1918	F.	..	.....	Fibrillation	Transient, 2 weeks	Hyperthyroidism	Digitalis	No fibrillation 4 months later
		M.	..	.....	Fibrillation	Transient, 2 weeks	Hyperthyroidism	Digitalis operation 20 days later	Fibrillation 9 days after digitalis, none 9 days after operation
White and Morris.	1918	F.	39	.....	Fibrillation, decompensated	Days	Goiter	Digitalis	Fibrillation ceased 2d day after digitalis
Mason	1920	F.	56	.....	Fibrillation	Attacks, many years	Exophthalmic	.....	.....
Crile and associates	1922	F.	47	.....	Fibrillation, decompensated	Paroxysmal, 16 months	Toxic adenoma	Digitalis operation 1 year later	Well for three years
Schwenson	1922	..	.	.....	Fibrillation	.....	Exophthalmic	Roentgen ray	Aggravated for 5 weeks, no fibrillation later
Schoonmaker and Webb	1922	F.	46	.....	Fibrillation	Permanent, 6 months	Toxic adenoma	Digitalis, operation	No fibrillation after digitalis, nor since
Baumgartner, Webb and Schoonmaker	1923	M.	49	.....	Fibrillation	Paroxysmal, 1 year	Toxic adenoma	Digitalis, operation	Fibrillation ceased after operation
		F.	51	.....	Fibrillation	1 previous attack, now established	Exophthalmic	Digitalis, operation	Death 1 day after operation
Hamilton	1922	6 cases		.....	Fibrillation	Paroxysmal, weeks	Hyperthyroidism	Digitalis, operation	No fibrillation after one, or both
		12 cases		.....	Fibrillation	"Established" weeks	Hyperthyroidism	Digitalis 4 and operation 8	Fibrillation still present in 3
						....	.....		1 death; 3 no fibrillation; 4 fibrillating

panied by irregular hearts. The latter stated that twelve were found in a series of 182 cases. Neither one gave any more definite statement, and in both the data was insufficient for diagnosing auricular fibrillation.

Mosse [14] gave a more detailed description of the case of a woman, aged 68, with exophthalmos and definite toxic symptoms. The pulse was described as irregular and small, with irregular heart action over several years. He discussed the frequency of irregular heart action in goiter and stated that in 128 cases of exophthalmic goiter only this one was found.

Sattler [15] described a case in a woman, aged 28, with definite symptoms of exophthalmic goiter and attacks of rapid irregular pulse. After rest in bed and sedatives she improved, but she had another attack three weeks later, then no more for two years, during which time her symptoms of goiter improved.

Hösslin [16] noted marked attacks of palpitation, tachycardia up to 240, and irregular pulse in a woman with severe exophthalmic goiter seen in 1901. These attacks continued until operation in 1906. The pulse was later perfectly normal in rate and rhythm. He also referred briefly to another patient with struma who had severe attacks of tachycardia with absolute arrhythmia following treatment with iodin.

Bamberger,[17] in discussing paroxysmal tachycardia in exophthalmic goiter, described three cases which were undoubtedly paroxysmal auricular fibrillation. One of these, in a man, aged 34, had attacks after administration of digitalis and after operation. In the other two cases, the treatment and result were not given. He said that the condition could not always be cured, and he noted that because of the irregular pulse these cases should not be classed with the usual paroxysmal tachycardias.

Fahrenkamp [18] briefly described an irregular heart "arrhythmia perpetua" in various conditions. In four cases, one a case of exophthalmic goiter, he found an intermittent arrhythmia, with a rapidly beating auricle and an arrythmic ventricle. The author does not use the term auricular fibrillation, although this term had been used by this time.

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14. Mosse, M.: Zur Kenntnis einiger seltener Störungen bei der Basedow'scher Krankheit, Berl. klin. Wchnschr. **44**:14, 1907.

15. Sattler, H.: Die Basedow'sche Krankheit, Leipzig, 1909, 1910.

16. Hösslin, R.: Die chirrurgische Behandlung der Basedowschen Krankheit, München. Med. Wchnschr. **56**:105, 1909.

17. Bamberger: Paroxysmal Tackykardia bei Morbus Basedowii, Deutsch. med. Wchnschr. **35**:1403, 1910.

18. Fahrenkamp, K.: Vorübergehende komplette Herzunregelmässigkeiten unten den klinischen Bilde der Arrhythmia perpetua mit Beobachtungen über Väguswirkung, Deutsch. Arch. klin. Med. **117**:1, 1914-5.

Krumbhaar [19] wrote on transient auricular fibrillation and stated that it occurred in infections, or toxic conditions, as hyperthyroidism. In another article,[20] he gives electrocardiograms taken in toxic goiters, and he briefly describes a few. One case is given in the table. In another case he mentioned (No. 10), the patient had had auricular fibrillation for ten years. Levine,[21] in a series of fibrillation cases seen at Boston, briefly mentioned one case which occurred in hyperthyroidism.

Since that time there have been several articles on auricular fibrillation in goiter. One by White and Aub,[22] was on electrocardiographic studies in thyroid disease. In forty-seven cases of hyperthyroidism, they found three patients with paroxysmal and three with permanent fibrillation—12.7 per cent. They give few details of individual cases. One patient with fibrillation and a pulse rate of 160 on December 20, was given digitalis, and on January 10 there was no fibrillation, and the pulse rate was 108. There was also no fibrillation when he was examined several months later. The first examination of a man on February 3 revealed a rapid pulse and no fibrillation, but this was present on February 16. Digitalis was given, but the patient still had fibrillation on February 25. Operation was performed on March 5, and the heart was normal when he was examined March 14 and on April 7.

White and Morris [23] in a paper on fibrillation incidentally mentioned thyroid conditions. One case of fibrillation cleared up the second day after digitalis therapy. In discussing transient or paroxysmal auricular fibrillation, Mason [24] gave these as occurring in 7 per cent. of 250 cases of fibrillation. In one, exophthalmic goiter attacks of fibrillation had occurred for years.

The case reported by Crile and his associates [4] is described in some detail. The patient had a toxic adenoma, was decompensated and fibrillating. She improved on digitalis therapy and other treatment, but she had four attacks the following year. She was then operated on and was well at the last report three years later.

In Hamilton's [5] series of 200 goiter cases, eighteen showed fibrillation, of which six were paroxysmal at frequent intervals throughout

19. Krumbhaar, E. B.: Transient Auricular Fibrillation, Arch. Int. Med. **18**: 263 (Aug.) 1916.

20. Krumbhaar, E. B.: Electrocardiographic Observations in Toxic Goitre, Am. J. M. Sc. **155**:175, 1918.

21. Levine, S. A.: Auricular Fibrillation: Some Clinical Considerations, Am. J. M. Sc. **154**:43, 1917.

22. White, P. D., and Aub, J. C.: Electrocardiogram in Thyroid Disease, Arch. Int. Med. **22**:766 (Dec.) 1918.

23. White, S. M., and Morris, R. E.: The Eggleston Method of Administering Digitalis, Arch. Int. Med. **21**:740 (June) 1918.

24. Mason, V. R.: Transient and Paroxysmal Auricular Fibrillation, Bull. Johns Hopkins Hosp. **31**:145, 1920.

months or years. All of the patients were cured of hyperthyroidism by operation and had normal hearts afterward. Digitalis had been used in these cases and some patients had shown normal hearts after its use before operation. In twelve patients there was "established" fibrillation, of whom four received only digitalis; three of these continued to have fibrillation. Of eight patients who had received digitalis and who had been operated on, four continued to have fibrillation.

Schwenson [25] stated that according to the Scandinavian literature, fibrillation in exophthalmic goiter subsided after operation. He reported a case which was aggravated at first by roentgen-ray treatment. Later a normal electrocardiogram was obtained. Kerr and Hensel [26] reported that auricular fibrillation and flutter occurred in one-third of 181 cases of goiter, of which 123 were adenoma and fifty-eight hyperplasia.

The earliest mention of conditions which were probably auricular fibrillation in goiter was made by Germain Sée [7] in 1878, who was struck by the fact that this irregularity of the heart had not been noted. Several other writers described conditions which we believe were auricular fibrillation. The first one given in our table (Griffith, 1886) possibly was not described in sufficient detail to be definitely classed as fibrillation. The same may be said concerning the second case described in 1890. The other case, we believe, can be accepted as cases of fibrillation. Bamberger, in 1910, gave definite descriptions of cases of paroxysmal fibrillation, and Krumbhaar, in 1918, first described the condition in this country. At the end of the table is included a series of cases by Hamilton in which age and sex are not given.

In analyzing the table we find that we have included twenty separate cases from 1886 to 1922; the sex was given in eighteen, and fifteen were females. In fourteen, the age ranged from 28 to 68, nine were in the fourth and fifth decades, and in six the age was not stated. The data bearing on fibrillation is given under pulses and heart columns for the earlier cases only. After auricular fibrillation was known and the word used, proof has not been given in our table. Fourteen of the patients had paroxysmal attacks, and only three had permanent fibrillation, while in five the data given was not sufficiently definite to justify the assignment of them to either class. No definite data were given in some of the cases as to how long patients had had attacks or had had fibrillation. The time mentioned varied from a few weeks to six years. Our first patient, judging from her history, had had fibrillation for six months; the second patient had had intermittent attacks for one year, and the

25. Schwenson, C.: Auricular Fibrillation in Hyperthyroidism, Ugesk. f. Laeger **84**:1756, 1922; abstr. J. A. M. A. **80**:518, 1923.

26. Kerr, W. J., and Hensel, G. C.: Observations of the Cardiovascular System in Thyroid Diseases, Arch. Int. Med. **31**:398 (March) 1923.

third, with an attack one year before, had had constant fibrillation for two months. Hoesslin and Bamberger's first patient had a history of attacks for from five to six years, but usually attacks had occurred only for several months or less before treatment was established.

As to the type of goiter in which fibrillations were described, in six the observers diagnosed exophthalmic goiter, and in five Basedow's disease, evidently, then, eleven cases of exophthalmic goiter in the eighteen cases. Probably five of the cases were toxic adenoma (one a nodular goiter); two were described as hyperthyroidism, one only as a goiter and one was not specified. In most of the cases it was not clear how long the patients had had goiters, nor how long these had given active symptoms. Our first and third patients had probably had goiter for ten years, with toxic symptoms at different times. The first had shown active symptoms for six months before entering the hospital, the second for one year, and the last, definite toxic symptoms for two months. Willius and Boothby [8] stated that patients with exophthalmic goiter with constant fibrillation had had goiter for a longer time than those with intermittent or transient fibrillation and longer than any of those with adenoma with hyperthyroidism.

Griffith,[8] using digitalis and iron, noted marked improvement, and stated that the eyes were normal three years later. Fibrillation ceased in two other cases after digitalis therapy. In six cases no treatment was recorded, in two of these frequent attacks of fibrillation continued, and the data were not definite in the remaining four cases. In Gerhardt's case strophanthus was said to have done no good, but the patient improved. The condition of the only patient treated with the roentgen ray was at first aggravated, but later fibrillation ceased. Sattler's patient improved on a treatment of bed rest and sedatives. Two patients continued to have fibrillation after administration of digitalis and operation, and three ceased to have fibrillation, one ceased to have fibrillation before operation. Two of our patients, one with constant fibrillation, and the other with intermittent fibrillation, became well after digitalis therapy and operation. In two cases the patients are recorded as normal or recovered after operation alone.

White and Aub mentioned having had three cases of paroxysmal and three cases of permanent fibrillation, but they give the details in only one case, as shown in the table. In Hamilton's cases diagnosed as hyperthyroidism, there were twelve patients with "established" and six with paroxysmal auricular fibrillation. Some were relieved by digitalis alone, some by digitalis and operation. Seven of the patients with established fibrillation did not become normal after either method of treatment or after both. Willius and Boothby gave some detail in seven cases of exophthalmic and two of active adenomas. All received massive doses of digitalis, and six of the seven were operated on, although in

one only a ligation was performed. In this one patient decompensation later occurred again; the remaining ones recovered. Both patients with adenoma recovered after digitalis therapy and operation.

DISCUSSION

Although auricular fibrillation as such was not definitely described until 1907, cases almost like this, if not the same, were described as occurring in cases of goiter as early as 1878. Few definite details were given about specific cases until 1910, although cases which we believe to have been fibrillation have been described since 1886. There are more cases in which there are paroxysmal attacks of fibrillation, although Hamilton had twelve patients with established fibrillation in his series of eighteen cases. Patients with transient cases may have attacks lasting for from a few hours to a day or more, coming on in days or weeks, and in one case described the patient had been having attacks for six years. The fibrillation may persist for years, as in the case described by Mosse. Willius and Boothby, as some others, have distinguished between intermittent and transient fibrillation.

In the twenty cases, probably eleven can be considered as exophthalmic goiter. Hamilton's cases were called hyperthyroidism with no distinction between exophthalmic goiter or toxic adenoma. The earlier writers used the term Basedow and did not distinguish between types as is now done. There can be no question that all were active cases of goiter or hyperthyroidism. Willius at the Mayo clinic found fibrillation in a higher percentage in the cases of adenoma. Two of our cases were adenoma. Undoubtedly this condition occurs in a higher percentage among women than among men, although Germain Sée stated that arrhythmias were more frequent in males. Hamilton found that patients with a history of tonsil trouble or rheumatism were more likely to have fibrillation than were others. There is no evidence of this in the other cases reviewed in this paper. Hamilton also found that fibrillation was more likely to occur in older people, in patients twenty years older than the average age of patients with goiter. The majority of cases here reported occurred in persons in the fourth and fifth decades.

In many of the later cases the electrocardiogram has been used to diagnose or prove the fibrillation. In a few of the earlier ones, pulse tracings served to give a clear enough idea. The description of definite palpitation—rapid, irregular hearts—in earlier cases was taken as evidence of fibrillation. It is rather strange that the condition was not noted earlier. However, despite the large percentages described by the Mayo and Boston clinics, smaller places either do not recognize the condition or it does not occur as often as these statistics show. The

condition has been diagnosed here three times in a clinic in which about fifty goiter operations are performed a year. Undoubtedly the goiter cases have a toxic origin, but whether there is definite myocardial damage, as Mason stated, is questionable.

As to prognosis, the results shown in the table would make one believe this good so far as the ultimate result is concerned, since eleven of the eighteen patients were either relieved entirely or markedly improved in both thyroid and heart conditions. Krumbhaar believed that an inverted "T" in the electrocardiogram was a bad prognostic sign. Others have also suggested this, while Willius and Boothby wish to limit this to negative "T" in certain leads only. In our first case there was a flat "T" wave in leads II and III about five weeks after operation, which became normal four months later; this one and the second case showed negative "T" in the same leads about three weeks after operation. White and Aub believed that the heart conditions did not parallel the basal metabolism figures, a view apparently held by Willius and Boothby. Our first patient here had a basal metabolism of 119 (by error this was reported as 199 per cent. in the *Clifton Medical Bulletin*), and the others 126 and 134 per cent. The latter patient, an exophthalmic case had a basal of 126 per cent. one week after the first one. In Hamilton's series patients with paroxysmal fibrillation have a better prognosis than those with established fibrillation. In our first case, a patient with established fibrillation, the condition cleared up completely.

Many cases have shown the value of digitalis therapy for fibrillation in goiter, as well as in other cases. Kerr and Hensel stated that the dosage required is less than for those in which fibrillation is due to other conditions. In two of our cases the condition cleared up on administration of only small amounts of digitalis and operation. Some of the cases have cleared up, i. e., fibrillation has ceased after digitalis alone. In some fibrillation has continued until after operation. In eight patients in this series who received digitalis or were operated on, or both, two continued to have fibrillation. Three patients treated with digitalis alone recovered. In Hamilton's series of four patients receiving digitalis, three continued to have fibrillation, and in eight patients with permanent fibrillation only three returned to normal, figures not as good as for the paroxysmal cases, since in fourteen cases here reported, nine cleared up complete and only in three did attacks of fibrillation continue. Lahey, in discussing Tinker's [27] article, stated that 30 per cent. if digitalized recover, with permanent cessation of fibrillation. Our figures here show that a greater percentage than this recover.

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27. Tinker, M. B.: The Desperate Risk Goitre, J. A. M. A. **79**:1291 (Oct. 14) 1921.

SUMMARY

Germain Sée, in 1878, described irregular, rapid pulse and heart in cases of goiter in which there was probably fibrillation. Twenty cases, besides a series of eighteen by Hamilton, and figures from other clinics have been reviewed. Fibrillation may occur in hyperthyroidism, in both adenoma and exophthalmic cases, and may be paroxysmal or permanent for months or years. These patients should be given digitalis as other patients with fibrillation are given it, and operation should be performed even if there is fibrillation. We believe, as was stated in Schoonmaker and Webb's report, that the "gravity of the heart condition relative to thyroidectomy has been repeatedly overestimated, resulting in delay in operation and in a borderline dangerous myocardial insufficiency."

LESIONS DUE TO THE BITE OF THE WHEEL-BUG, ARILUS CRISTATUS (HEMIPTERA; REDUVIIDAE)

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In the fall of 1922, my youngest daughter (M.L.H.), aged 10, captured a wheel-bug, *Arilus cristatus* (determined by W. L. McAtee), at Chevy Chase, D. C., and was bitten twice by it on the inner aspect of the little finger of the right hand at a point near the nail. The finger became reddened and felt hot to the touch. In the course of a few days, growths resembling papillomas developed at the sites of the punctures, the largest of these projecting as a small hornlike structure. Both of these growths persisted for months, the largest slowly disappearing between six and nine months after the infliction of the bite. The injured finger remained warmer than the other fingers during this period, and, according to the patient's statement, still feels warmer than the other fingers, a year later. The development of pronounced cutaneous growths after a bite appears indicative of the action of some toxin as a stimulant irritant.

Over thirty species of Heteroptera have been reported as attacking man. Of the genera reported in this connection from North America may be mentioned *Cimex*, *Opsicoetes* (*Reduvius*), *Apiomerus*, *Triphleps*, *Arilus* (the species in question), *Conorhinus*, *Rasahus*, *Melanolestes* and *Reduviolus*.

Tissue growths such as "galls," following injuries due to insects, mites, nematodes, etc., are not uncommon in plants. In animals, tissue growths due to parasitic nematodes are not uncommon, and in the case of one nematode, *Gongylonema neoplasticum*, infestations with the worm produce true malignant neoplasms with metastases in tissues other than those invaded by the worm. Tissue growths following the bites of insects appear to be uncommon in animals.

Some of the symptoms and lesions which have been reported in cases of persons bitten by so-called "kissing bugs" and related forms are as follows: The bite is followed by intense pain, extending from the bitten finger to the head, and followed by a feeling of faintness, with recovery in less than half an hour except for slight local cellulitis (Herms); intense pain, the swelling and irritation lasting for a week (LeConte, quoted by Howard. LeConte adds: "In very weak and irritable constitutions it may even prove fatal," but it is not clear from the wording whether this statement refers to actual cases or to possibilities); a burning pain, intense itching and much swelling, with the appearance

of red blotches and welts all over the body and limbs, the effects lasting for months or disappearing in a few days (Marlatt); nausea, flushed face, palpitation of the heart, rapid breathing, rapid pulse, followed by profuse urticaria all over the body, the intensity of reaction varying with different individuals (Herms); appearance the day after the bite of a local cellulitis with a dark central spot, around which frequently appears a bulbous vesicle the size of a 10-cent piece and filled with a dark grumous fluid, followed by the formation of a small ulcer with a central necrotic area, the surrounding tissues more or less swollen and painful, and the swelling subsiding in a few days and followed by recovery in the course of a week (Davidson, quoted by Howard); pain, followed by numbness (Lintner, quoted by Howard); pain, followed by swelling, or swelling with but little pain (Howard); pain, rapidly increasing in severity and extending up the arm to the lower jaw, followed by slight swelling and no further inconvenience (Howard); serious illness, with recovery lasting almost a year (LeConte, quoted by Howard); inflammation with the arm almost useless for three days after the infliction of three bites (Osborn).

An inspection of the foregoing shows that the local reactions may include a sharp pain rapidly diminishing in intensity or rapidly increasing in intensity and extent, numbness, local inflammation lasting a short time or persisting for months, swelling which may be transient or persist for a week or longer, itching, vesicle formation, ulceration, necrosis and, in the present case, formation of tissue growths resembling papillomas; while the general reactions may include extension of pain from the finger to the head, faintness, generalized urticaria, which may be transient or may persist for a long period, nausea, flushed face, palpitation of the heart, rapid breathing, rapid pulse, vomiting or serious illness requiring almost a year for complete recovery.

The case reported here was presented before the Entomological Society of Washington, and in the discussion Dr. E. A. Schwartz and Mr. A. N. Caudell stated that they had been bitten by *Arilus cristatus* and that the bite was the most painful of injuries either of them had ever sustained from insects. In Mr. Caudell's case, the bite was under the thumb nail and caused intense pain for an hour, and in both cases the unpleasant effects lasted for several days.

A consideration of the fact presented here leads to the following theories as to the relationship between the bites of these bugs and the resulting symptoms and lesions. In some cases, the mechanical puncture and the injected toxin cause local pain, usually very severe, but sometimes comparable to that usually experienced from bee stings; and in such cases it might be assumed that the toxin injected was not very powerful or the patient actually or relatively tolerant of it, or that the

injection was subcutaneous but not intramuscular or directly into the blood vessels. In other cases, the bite causes severe systemic reactions, sometimes lasting for long periods, and in such cases it might be assumed that the toxin was very powerful or the patient distinctly intolerant of it, or that the injection was intramuscular or directly into the blood vessels. In this connection, it may be said that the long and powerful piercing beak of these bugs is capable of entering the relatively large and superficial veins of the hand and arm. In the case here reported, the development of papillomatous skin growths at the site of puncture might be referred to the stimulant irritant action of a toxin injected intradermally, giving rise to a pronounced local reaction with practically no systemic effects. The insect bit twice in rapid succession, causing pain of only moderate severity, not severe enough to discourage the patient in her attempt to capture the insect, and did not draw blood. While I have found no similar case in the literature, in a casual survey, it appears likely that a similar result would be produced under similar conditions; i. e., an intradermal injection of toxin in lieu of the usual deep puncture inflicted by the insect. That the bites of the large bugs are ordinarily deep enough to draw blood is evident from the fact that certain species of the genus *Triatoma (Lamus)* especially *T. megistus* are the carriers of the trypanosome causing Brazilian trypanosomiasis of man, Chagas' disease. The bites of these carriers, like those of the bed bug, are commonly much less painful than those of such bugs as the wheel-bug, which, as a rule, bite only when molested

THE SKIN-REACTION TO MORPHIN *

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Solutions of morphin and its esters, when introduced into the skin, produce local reactions, consisting of the urticarial wheal with an erythematous areola (Sollmann and Pilcher [1]). The lesions are quite like those formed in susceptible individuals by the local inoculation of foreign proteins, and in probably all individuals by inoculation of histamin or any one of a series of definite chemical substances (Sollmann [2]).

This local reaction to the morphins raised a number of interesting questions, some of which will be considered in this paper. Perhaps the most important of these concerns the possibility of the modification of the local reaction by habituation. Does the high degree of tolerance to the toxic actions of the morphins that is acquired by addicts extend also to the local reactions? or, stated conversely, does the local reaction vary with changes in the systemic susceptibility, as is the case with desensitization or "habituation" to the protein poisons? The answer to this question is not only of scientific interest, but if it were to be positive, it might have a great practical value for the diagnosis of opiate addiction. Unfortunately, from this point of view, the answer is in the negative. The local reaction is not at all modified by the acquirement of the systemic tolerance; it is the same in patients during the various stages of habituation and dishabituation, as it is in normal individuals. Scientifically, this result is of interest in confirming the fact that the acquired tolerance does not extend to all the effects of morphin; but that it is confined to certain functions.

As regards central actions, Van Egmond [3] found that tolerance was acquired in the order of pupils > emesis > defecation > narcosis > respiratory center; while no tolerance was acquired toward the central vagus action. Langer [4] also failed to produce any tolerance to the convulsant action of diacetylmorphin. Apparently, the tolerance involves only the psychical inertia and its secondary results, among which should probably be included the miosis, the constipation, and the respiratory depression that is the immediate cause of the fatality. It is natural

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* From the Department of Pharmacology, Western Reserve University School of Medicine.

1. Sollmann, Torald, and Pilcher, J. D.: J. Pharm. & Exper. Therap. **9**:309 (March) 1917.
2. Sollmann, Torald: Jour. Pharm. & Exper. Therap. **9**:391 (April) 1917.
3. Van Egmond, A. A. G.: Arch. Exper. Pathol. & Pharm. **65**:197, 1911.
4. Langer: Biochem. Ztschr. **45**:221, 239, 1912.

to conceive that this psychical inertia could be compensated relatively simply by the gradual education of psychic adjustments. The acquired tolerance to the emetic action could also be explained on a psychic basis. The vagus and convulsive centers and the local inflammatory actions lie entirely outside of the psychic sphere, and, therefore, could not be corrected by psychic compensations.

It may be added that it is also impossible to desensitize locally to morphin or histamin by repeating the applications at ten minute intervals (Sollmann [5]); a method that desensitizes the *specific* hypersusceptibility of the protein of foods, etc. (Mackenzie and Baldwin [6]).

When the morphin skin-test is made by intracutaneous injections, as will be described, the response is remarkably uniform in the great majority of subjects, normal or addicts. No significant differences are found between males and females, or between the white and colored races. A few individuals gave a moderately exaggerated reaction, but these also gave a similarly exaggerated reaction to the control injection of physiologic sodium chlorid solution; i.e., their skin was hypersensitive to irritation in general, and not especially to the morphin irritation. It is probable that patients with a true "idiosyncrasy" toward morphin show a highly exaggerated and specific reaction; but none of these came under observation.

On the other hand, preexistent edema of the skin masks the reaction to morphin; so that the latter may perhaps even serve as a test for the existence of edema, or indeed generally for the condition of the skin, its delicacy and irritability.

METHODS

The intradermal method was used in preference to the scratch methods, since the former not only acts with much smaller concentrations, but also permits a much better control of the quantity of solution introduced into the skin, and therefore gives more uniform results. The injections were made into the cutis of the flexor surface of the forearm, a sufficient quantity of the solution being introduced to produce an immediate distention wheal about 5 mm. in diameter. A control wheal was made with physiologic sodium chlorid solution containing 0.25 per cent. of tricresol; and the course of this was compared with that of strictly similar wheals produced by the solution with the addition of morphin hydrochlorid, in the proportions of 1:1,000, 1:100,000 and 1:1,000,000. The latter solution gave either no reactions beyond that of the saline control, or only a minimal increase. The

5. Sollmann, T.: J. Pharm. & Exper. Therap. **9**:147 (Jan.) 1917.

6. Mackenzie, G. M., and Baldwin, L. B.: Local Desensitization in Hypersensitive Individuals and Its Bearing on Prevention of Hay-Fever (Arch. Int. Med. **28**:722 (Dec.) 1921.

1:100,000 solution always gave mildly positive reactions. With the 1:1,000 the response was always so marked that it was deemed superfluous to employ more concentrated solutions. This illustrates the lower sensitiveness of the scratch method, which gives at most slight reactions with the 1:1,000 solutions. A number of experiments were also made with a 1:10,000 solution, but as this gave no additional information, its use was discontinued. The total quantity of morphin introduced at a complete test, comprising three injections, is about 0.1 mg. (1/600 grain), so that there is no possibility of any perceptible systemic effect whatever; nor was any such effect ever noticed by either normal subjects, addicts, or exaddicts.

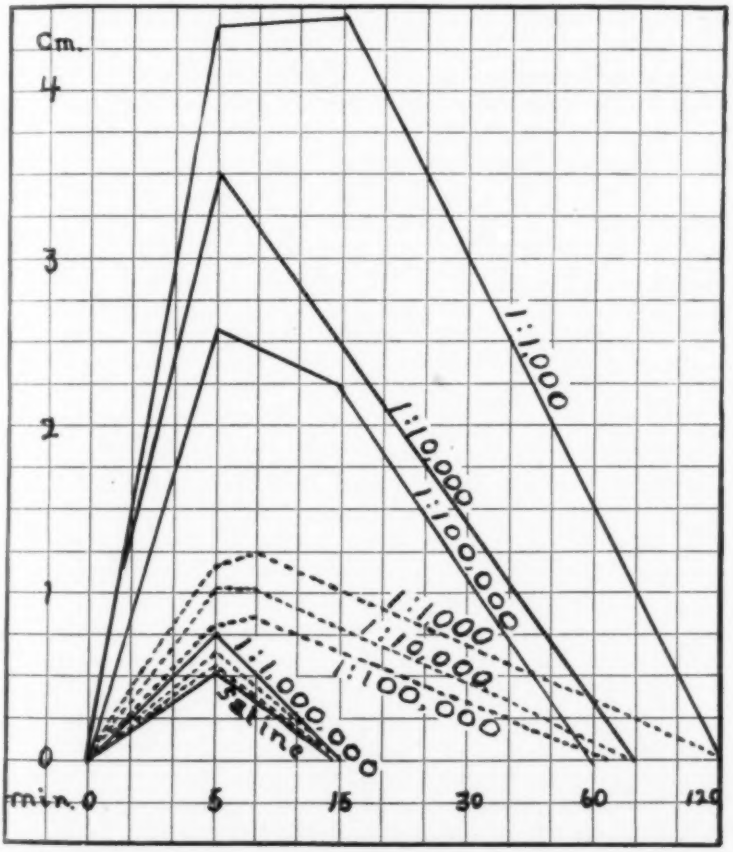
OBSERVATIONS

The injection sites were usually observed at five, fifteen, thirty, sixty and 120 minute intervals following the injection, the size of the wheal and of the erythematous area being measured. As the reactions subside, the outlines of the wheals and, to a less extent, of the areola become less and less distinct, so that accurate measurements are impossible. The reactions were then recorded as "fading" or "faded."

Normal Course of the Morphin Reactions.—As has been stated, this is remarkably uniform, although minor quantitative variations are found, even in the same individual; for one thing, because it is not practical to introduce exactly the same quantity of the solution into the same area of skin. These accidental variations may be smoothed out by multiplying the observations; and since the conditions observed by us did not modify the course of the reactions, we may employ the medians of the entire series of about eighty subjects as a basis for the "normal course." The phenomena are most typical when they are most marked, i.e., with the 1:1,000 solutions.

Course of the Reaction to the 1:1,000 Solution.—There is a momentary stinging sensation, but exceptionally a little pain. Then the primary 5 mm. wheal, produced mechanically by the intracutaneous injection, becomes rapidly reddened, increases in size and is surrounded by a congested area of rather irregular outline. The maximum intensity is reached in from five to ten minutes, seldom later. The wheal is then about 12 mm. in diameter, somewhat doughy, moderately raised above the surrounding skin, rather sharply circumscribed and fairly circular, but sometimes having a few pseudopods. It is surrounded by an erythematous areola having the diameter of from 4 to 6 cm.; bright or "angry" red near the wheal, paler and somewhat mottled toward the periphery. Usually the size of the wheal and the congested area were roughly proportional; i.e., the larger the wheal, the larger the congested area. There were exceptions, as illustrated by two experiments with

the 1 : 1,000 solution: One subject, aged 55, had a wheal 1.6 cm. and a congested area 4 cm. in diameter; while a second subject, aged 23, had a wheal 1 cm. and a congested area 6.8 cm. in diameter. This variation is probably due to want of parallelism between the permeability and dilatation of the skin capillaries.



Course of morphin (composite of all experiments). The curves represent the median diameter of the wheals (broken line) and areolas (solid line). The diameter is given in centimeters; the time after injection in minutes.

Subsequent Course.—Usually within fifteen minutes after the injections, the phenomena begins to subside. The wheal becomes flatter and paler, and its borders are less distinct. The areola decreases in size and color. The fading progresses rather slowly. In an hour after

the injection, the areola is quite faint, and the site of the wheal pale, and still indurated, but not elevated above the surrounding skin. Somewhat later, one and one-half or at most two hours after the injection, all visible trace of the reaction has disappeared.

Reactions to the More Dilute Solutions.—These differ from those just described merely in intensity and duration, these two being fairly parallel. Their course is shown graphically in the accompanying figure.

Morphin Addicts Examined.—The addicts used in this study included a small group who were receiving known quantities of morphin from the Narcotic Bureau; and a larger group of inmates of the "House of Correction" undergoing the treatment by rapid withdrawal of the drug. There is no doubt that all the subjects of both groups were confirmed addicts, with considerable tolerance. All but two (and these had been receiving known quantities from the Narcotic Bureau) bore the scars of hypodermic punctures; and with few exceptions, the scarring was quite extensive. All except these two stated that they took their drug hypodermically, a very few by severely scratching the skin and rubbing the alkaloid into the wound. The conditions were therefore optimal for acquiring not only a systemic but also a local tolerance to the morphin.

A record was kept of the statements of the subjects as to the duration of their addiction and their normal dosage. The majority claimed that they had taken the drugs for many years, the average being at least ten years, with extremes of from a few months to forty-one years. Many were physically much below normal. Those who had been without the drugs for some weeks were usually in excellent physical condition. Their ages ranged from twenty to seventy-four years. The mean of the claimed daily dosage was between 10 and 15 grains (0.65 and about 1.00 gm.) of morphin or "heroin" (diacetylmorphin), with extremes of from 5 to 90 grains (0.32 to 5.85 gm.). The addicts were generally very willing to furnish these data, but as they may be easily influenced by the hope of securing a larger supply or slower withdrawal little use was made of their direct statements. Other evidence is adequate to establish their tolerance. Those supplied by the Narcotic Bureau received from 3 to 5½ grains (0.19 to 0.35 gm.) of morphin sulphate daily from that source. Many others had received a controlled dose before their admission to the House of Correction, and their tolerance was manifest from the degree of their response.

Classification of the Subjects.—In view of the unreliability of the exact degree of habituation, it seems scarcely worth while to classify the subjects from that point of view. The arrangement actually adopted accords with the stage of the treatment.

Group A: Current addition: Five subjects who were receiving from 3 to 5½ grains of morphin a day from the Narcotic Bureau.

Group B: Abstinence symptoms: Eighteen subjects still receiving morphin or diacetylmorphin in reduced, but still large dosage (usually from 1 to 4 grains (0.065 to 0.260 gm.) on the day preceding the test), and showing abstinence symptoms, slight in about two-thirds of the patients, severe in the others.

Group C: Complete withdrawal (short, i. e., of from ten to twelve days): Ten subjects. Abstinence symtoms had completely disappeared.

Group D: Complete withdrawal (intermediate, i. e., of from two to ten weeks): Nine subjects.

Group E: Complete withdrawal (long, i. e., of from six to seven months): Nine subjects.

TABLE 1.—*Comparison of Intradermic Morphin Test in Addicts and Nonaddicts**

	Morphin Hydrochlorid 1:1000				Morphin Hydrochlorid 1:100,000				Morphin Hydrochlorid 1:1,000,000			
	Wheal		Areola		Wheal		Areola		Wheal		Areola	
	5 Min.	30 Min.	5 Min.	30 Min.	5 Min.	30 Min.	5 Min.	30 Min.	5 Min.	30 Min.	5 Min.	30 Min.
Nonaddicts:												
Group I.—Normal.....	12.5	F	43	37	9	F	30	F	+	0	0	0
Group II.—Therapeutic.....?	—	F	—	F	—	F	—	F	—	0	—	+
Addicts:												
Group A.—Current addicts..	12	F	40	F	10	7	30	F	+	0	+	F
Group B.—Abstinence symptoms.....	12	F	44	F	8	F	16	F	+	0	+	0
Exaddicts:												
Group C.—10 to 12 days.....	11.5	F	43	F	8	F	17	0	+	0	0	0
Group D.—2 to 10 weeks.....	12	—	45	—	8	—	27	—	0	—	0	—
Group E.—6 to 7 months....	12	F	50	42	8	F	25	F	0	0	+	0
General average of all groups	12	F	44	F	8	F	26	F	+	0	+	0

* The numbers correspond to the median diameter in millimeters of the wheal or areola in addicts, exaddicts, and nonaddicts; F indicates that the response has faded materially; 0, that it had disappeared practically completely; + indicates a positive reaction, but too slight for measurement.

For comparison with these, we have two groups of nonaddicts:

Group I, normal: Seventeen normal individuals who had never used opiates habitually, and many of whom had never received effective doses even therapeutically.

Group II, therapeutic: Four subjects who had never been addicted to opiates, but who for therapeutic purposes had received several small doses in the hospital on the days preceding the test.

The comparative results as to intensity and duration of the reaction may be illustrated by the observations for from five to thirty minutes after injection, as shown in Table 1. The data for all the other periods have been similarly tabulated, but need not be reproduced, as they merely confirm the conclusions in Table 1.

A glance at the table shows the identity of the figures in each vertical column; i.e., the identity of the reaction of all the groups, as concerns the maximal or the minimal concentrations, or the intensity or duration of the response.

Table 2 illustrates that the extremes, as well as the medians, are uninfluenced by habituation.

TABLE 2.—*Extreme Variations of the Morphin Reactions* *

	Wheals	Areola
Nonaddicts	11-18	20-65
Addicts:		
Group A	14-14	30-45
Group B	9-20	14-60
Exaddicts:		
Group C	10-18	30-60
Group D	10-20	40-60
Group E	9-13	65-67

* Measurements (mm.) 15 minutes after injection of a 1:1000 solution. The lettering of the groups is as in Table 1.

COMPARISON OF THE MORPHIN TEST OF WHITE AND COLORED RACES

Whether the greater resistance of the negro-skin to certain irritants, such as light, and dichlordiethylsulphide, extends also to morphin seemed worth investigating. We utilized thirteen negroes of light to very dark skins belonging to various addiction groups; but as we have shown that addiction does not alter the response, they may all be grouped together. The results are shown numerically in Table 3. Only the numbers for the wheals of the five-minute period are reproduced.

The wheal response is evidently identical. The color of the areola cannot be differentiated sharply from the dark color of the surrounding

TABLE 3.—*Median Diameter (Mm.) of Wheal After 5 Min.*

	Morphin Hydrochlorid		
	1:1000	1:100,000	1:1,000,000
White	12	8	0
Colored	12	9	0+
General average	12	8	+

normal skin of the negro, although it can be seen somewhat dimly. In the lighter mulattoes, the reaction is sufficiently visible for measurement, and then averages the same as in the white race.

INFLUENCE OF SEX

The results in thirty-nine males and nineteen females were tabulated and found to be almost identical. Actual figures show a somewhat smaller wheal and a somewhat larger areola in females. For instance, five minutes after the injection of the 1:1000 solution, the wheals

average 12 mm. in the males, 11.5 in the females; the areolae, 40 mm. in the males, 45 in the females. These differences are within the range of statistical variations. They might, however, represent a true difference in reaction, due to differences in the structure of the skin or the responsiveness of the capillaries to irritation. We have the impression that fine or delicate skins, regardless of sex, gave a greater reaction than thick, dense skin. A majority of the subjects that gave reactions above the average were noted as having fair skins; but exceptions to this were numerous.

Age has no apparent influence in the morphin response.

THE EFFECT OF EDEMA

The test was applied to three subjects, not addicts, who had edemas secondary to cardiac insufficiency, their edema varying from slight to an extreme degree. In these subjects, the reaction was distinctly less than in the normal individual, as to both the size of the wheal and of the congested area, and the rate of disappearance. The greater the edema, the less was the reaction. With slight edema, the reaction was similar to the normal, but persisted for a shorter time; with moderate edema, the injection wheal formed, increased but little in size and soon faded; with edema so extreme that fluid oozed from the needle puncture, no wheal could be formed even with a 1 per cent. morphin solution. The erythematous area was slight in one case, and could not be seen in a second as the subject was a negress. In the subject with extreme edema, an approximately normal congested area was present, which was of somewhat lesser duration, and no increase in congestion was noted with the 1 per cent. solution. The diminished response in the presence of the edema might be due to the rapid dilution or dispersion of the solution. It is more likely that a tissue already edematous cannot swell much more, and capillaries that are compressed by edema cannot dilate effectively.[7]

In any case, the edema must be actually present if it is to check the morphin reaction; for practically normal wheals and areolas were obtained on two boys, one with severe chronic nephritis and the other with cardiac insufficiency (aortic insufficiency and myocarditis), who were not edematous at the time, although each had been so formerly.

CONCLUSIONS

1. Morphin administered intradermally produces a wheal surrounded by a congested area, the reaction increasing in intensity and duration

7. Since the foregoing was written, we note that W. B. McClure and C. A. Aldrich (Time Required for Disappearance of Intradermally Injected Salt Solution, J. A. M. A. **81**:293 [July 21] 1923) recently described a similar phenomenon, edema hastening the rate of disappearance of the induration produced by the intradermic injection physiologic sodium chlorid solution.

with the concentration. The minimum concentration of 1:1,000,000 was effective in about one half the experiments. A 1:100,000 solution always produces a wheal and congested area.

2. The reaction reaches the maximum in from five to fifteen minutes and disappears in from one to two hours.

3. The reaction is in every respect the same in addicts and in normal individuals. Systemic tolerance of morphin, therefore, does not induce local (skin) tolerance.

4. The reaction is idential in the young and in old adults; in males and females; in the white and negro races.

5. The reaction is probably somewhat more marked in skins of fine texture.

6. The presence of edema greatly lessens the wheal formation, and in extreme cases of edema, abolishes it.

THE P_H AND BUFFER VALUES OF DUODENAL CONTENTS DERIVED FROM NORMAL MEN *

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AND
L. L. CAMPBELL, PH.D.
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The present communication reports the results obtained from a study of p_H and buffer values, the latter determined by electrometric titration, of duodenal contents derived from normal persons.

With the exception of the comparatively recent publications of McClendon [1] and of McClure [2] and their co-workers, there are no reported studies on the p_H of duodenal contents collected during the period when intestinal digestion was definitely known to be in progress. The paucity of observations of this nature led us to make a somewhat more comprehensive study of the subject.

EXPERIMENTAL PROCEDURE

For the purposes of the recent investigation, duodenal contents were obtained from normal young men. The duodenal tube was taken before breakfast, fifteen hours after the last food intake and nine hours after the last drink of water. The tip of the tube was allowed to pass into the priximal end of the second portion of the duodenum, a distance of from 5 to 10 cm. from the pyloric sphincter, the position being determined by fluoroscopy. The subject then ate a meal consisting of either a pure protein (edestin), a pure fat (olive oil), a pure carbohydrate (arrowroot starch), or a mixture of these substances. Before ingestion, the edestin was thoroughly moistened with water, and the arrowroot starch was cooked in boiling water until a thick gelatinous, translucent mass was obtained. Twenty-five grams of each substance constituted a meal; and in order to make the desired volume, 25 c.c. of water was shaken with the olive oil just prior to its ingestion. The meal composed of a mixture of the three food substances contained 8.33 gm. of each of them. After the ingestion of a meal, the subject reclined on the right side and duodenal contents were collected by siphonage over the

* From the Evans Memorial and the Department of Physics, Simmons College.

1. McClendon, J. F.; Bissell, F. S.; Lowe, E. R., and Meyer, P. F.: Hydrogen-Ion Concentration of Contents of Small Intestine, J. A. M. A. **75**:1638 (Dec. 11) 1920.

2. McClure, C. W.; Wetmore, A. S., and Reynolds, L.: Physical Characters and Enzymatic Activities of Duodenal Contents; Findings During Gastric Digestion in Normal Young Men, J. A. M. A. **77**:1468 (Nov. 5) 1921.

following periods: (1) from the time of ingestion of food up to the abrupt appearance of very dark colored bile; (2) over the succeeding period of thirty minutes; and (3) over a second half-hour period. During the first period of collection, intestinal digestion was at its minimum; while during the second and third periods, intestinal digestion was in its normal degree of activity. In certain experiments, duodenal contents were collected before the ingestion of food. In other experiments, collections were made over two successive thirty-minute periods after the ingestion of 50 c.c. of tap water. All duodenal contents were collected in flasks immersed in ice water.

The apparatus employed in the determination of the p_H of duodenal contents consisted of a Leeds and Northrup potentiometer, a D'Arsoval galvanometer, a standard Eppley cell, a calomel half-cell, a hydrogen electrode and a special titration vessel of the conical Bovie type. Into this vessel were inserted the hydrogen electrode, the capillary tube from the calomel cell and a thermometer. The advantage of the conical cell is that the material in it may be thoroughly mixed by the inflow of hydrogen.

The hydrogen electrode consisted of a straight glass tube in which was sealed a fairly large, straight platinum wire that projected about 1.5 cm. from the sealed end of the glass tube. This tube was inserted in the hydrogen delivery tube so that the inflow of hydrogen completely bathed the platinized end of the wire. The wire was platinized in a 5 per cent. solution of platinic chlorid, thoroughly washed and hydrogenized in a solution of sulphuric acid and then washed free from acid.

The calomel half-cell was constructed in accordance with the usual standard specifications. The end of the potassium chlorid capillary tube leading from the calomel cell and entering the titration vessel was drawn down to a smaller diameter and bent into a J shape. This caused the lower, open end to point upward in the titration vessel, which minimized convection and diffusion of liquids in the tube and vessel.

The reliability of the apparatus was frequently tested by measuring the electromotive force between the calomel cell and the hydrogen electrode in a solution of hydrochloric acid of known normality and p_H. During all determinations, there was no evidence of the electrode being "poisoned."

The p_H of the duodenal contents was determined shortly after the duodenal contents were collected, and at room temperature in the neighborhood of 20 C. Between determinations, the contents were kept in a refrigerator at ice temperature.

The buffer values of the duodenal contents were determined by titrating 50 c.c. of the contents with tenth normal hydrochloric acid or

sodium hydroxid solution, according to whether the original material was alkaline or acid. The resulting p_H values were determined up to and beyond the neutral point. Curves of these values were plotted against the amount of acid or alkali, and the amounts needed to bring the p_H values to 7 were read from the curves.

The buffer values of the duodenal contents were computed from the equation developed by Van Slyke[3]: $\beta = \frac{\Delta B \text{ or } \Delta A}{\Delta p_H}$

Δ B, or Δ A, is the amount of tenth normal alkali or acid solution required to neutralize 1 c.c. of duodenal contents; or Δ B, or Δ A, $= \frac{V}{V'} \frac{N}{10}$ in which V is the volume of the alkali or acid used; N the normality of the solution and V' the total volume of the original duodenal contents in the titration vessel. The total change in the p_H value from the original to the neutral state is Δp_H.

The β values in the tables of the present report are average values, since the amount of acid or alkali required to effect a change in the p_H value by 1 varies for different H-ion concentrations in the same material. The buffer value of a given specimen of duodenal contents was estimated from the foregoing equation only when the titration curves of the p_H change against the amounts of alkali or acid added formed fairly straight lines.

EXPERIMENTAL DATA

The p_H was determined in fasting duodenal contents and in those collected after the ingestion of 50 c.c. of tap water. The collections were divided in periods of thirty minutes each. The term fasting duodenal contents designates the contents of the duodenum about fifteen hours after the last food intake and nine hours after the last drink of water. But in taking the tube, subjects swallow much saliva. It is also well known that the normal fasting stomach contains more or less acid secretion, cellular débris and mucin. Undoubtedly, the stomach throws these materials over into the duodenum, so that there was not a truly fasting state of the stomach during the course of the experiments reported here. Previous work has shown that the concentrations of pancreatic enzymes and of bile in duodenal contents are the same in contents obtained after water drinking as in those removed from the "fasting" duodenum. The results of the present study are outlined in Table 1.

A perusal of Table 1 shows that the p_H of the duodenal contents of a fasting subject was either above or below 7; while that of those derived from water were above 7. These duodenal contents were all pale yellow and of slight viscosity.

3. Van Slyke, D. D.: J. Biol. Chem. **52**:525 (June) 1922.

The p_H of duodenal contents was determined in those collected from immediately after the ingestion of food up to the time of the abrupt change from pale yellow to a very dark color occurred. During this period, no stimulating effect of the ingestion of food on the flow of bile or pancreatic juice had yet occurred. The results are outlined in Table 2, which shows that the p_H of duodenal contents collected under the conditions described may be either above or below 7. These contents were all light yellow and of slight viscosity. The duration of the

TABLE 1.—*P_H and Buffer Values of Duodenal Contents Collected Over 30-Minute Periods, Either While the Stomach was Fasting or After the Ingestion of 50 c.c. of Tap Water*

		Buffer Values		
Subject	p_H	No. of C.c. N/10 HCl or NaOH to Bring 1,000 C.c. Duodenal Contents to p_H 7	β (buffer) Values: No. of C.c. N/10 HCl or NaOH to Change p_H Value 1,000 C.c. Duodenal Contents by Unity	State of the Stomach
B	8.075	180	167	Fasting
C	6.727	...	...	Fasting
I	8.264	...	...	50 c.c. tap water ingested
A	7.579	...	...	Fasting
	7.588	...	...	1st 30 minutes after water ingestion
	8.093	...	...	2d 30 minutes after water ingestion

TABLE 2.—*P_H and Buffer Values of Duodenal Contents Collected from Immediately After the Ingestion of Food up to the Onset of Intestinal Digestion*

		Buffer Values		
Subject	p_H	No. of C.c. N/10 HCl or NaOH to Bring 1,000 C.c. Duodenal Contents to p_H 7	β (buffer) Values: No. of C.c. N/10 HCl or NaOH to Change p_H Value 1,000 C.c. Duodenal Contents by Unity	Kind of Food Ingested
B	6.240	110	144	Olive oil
	7.811	180	222	Edestin
C	6.937	...	...	Olive oil
	7.485	98	202	Edestin
	5.961	...	...	Olive oil, edestin and arrowroot starch

periods of collection varied from eight to thirty-nine minutes. During the collection of these specimens, food appeared in them within the first few minutes.

Tables 1 and 2 deal with duodenal contents collected over periods during which the stimulating effect of food on the flow of bile and pancreatic juice was not present,[4] as will be discussed later. Table 3 presents the results obtained from a study of the p_H and buffer values of duodenal contents collected during periods when the stimulating effect of food on the flow of pancreatic juice and bile was present, as will also be discussed later.[4] This effect began with the change from

4. McClure, C. W., and Wetmore, A. S.: Boston M. & S. J. **187**:882 (Dec. 14) 1922.

the initially light yellow colored bile to a very deep colored bile. The findings in these duodenal contents are outlined in Table 3, a study of which shows that in both subjects duodenal contents derived after the ingestion of either olive oil or arrowroot starch were alkaline (p_H above 7); while those collected after ingestion of edestin or the mixture of food substances were acid (p_H below 7). These duodenal contents were all some shade of dark yellow and of moderate viscosity, and all contained food.

The figures for buffer values which are presented in the tables, with their significance and also that of the p_H values will be discussed under separate headings.

TABLE 3.—*P_H and Buffer Values of Duodenal Contents Collected Over Two Consecutive 30-Minute Periods After the Onset of Intestinal Digestion*

		Buffer Values		
Subject	p_H	No. of C.c. N/10 HCl or NaOH to Bring 1,000 C.c. Duodenal Contents to p_H 7	β (buffer) Values: No. of C.c. N/10 HCl or NaOH to Change p_H Value 1,000 C.c. Duodenal Contents by Unity	Kind of Food Ingested
B	7.163	26	150	Olive oil
	8.102	169	153	
	5.101	324	172	Edestin
	3.172	710	185	
	7.013			
	7.971	223	230	Arrowroot starch
	6.806	76	392	Olive oil, edestin and arrowroot starch
	6.879			
O	7.011	...	...	Olive oil
	6.743	36	140	Edestin
	6.684	66	200	
	7.178	...	...	Arrowroot starch
	7.745	91	122	
	6.367	174	275	Olive oil, edestin and arrowroot starch
	6.000	250	250	

BUFFER VALUES

Enzyme action is profoundly affected by the hydrogen-ion concentration of the medium in which the active principle is either suspended or dissolved; and the maintenance of the p_H value of the medium is conditioned in large measure by the concentration and efficiency of the buffer substances present. Buffer conditions are included in the present report as a part of the examination of the duodenal contents, and the values obtained are collated in Tables 1, 2 and 3.

Some years ago, Van Slyke [3] published an interesting generalization in which he defined as the buffer value β the relationship of the amount of acid respectively alkali necessary to produce a change of 1 in the value of the p_H. The equation developed by Van Slyke has already been described in this article. An inspection of the conditions shows that at best this buffer value as computed for duodenal contents would

be only an approximation of an empiric relationship, and in the extreme cases could range from limits of zero to infinity in magnitude.

In the present study, the titrable acidity or alkalinity has been determined by bringing a definite quantity of the duodenal contents to the neutral point by the addition of standard acid or alkali, the choice governed by the initial reaction of the duodenal contents; p_H values were determined initially and the neutral point evaluated by further potentiometric comparisons, after addition of successive portions of the titration solutions. By dividing the number of cubic centimeters of the titration fluid with the numerical expression of the p_H range involved in the titration, an empiric value has been derived somewhat analogous to the β value of Van Slyke.

When calculated on the basis of a change of one in the value of the p_H, the buffer values for duodenal contents are surprisingly uniform (Tables 1, 2 and 3), there being evidences of an almost linear relationship.

The presence of olive oil would not influence the titration value of duodenal contents on addition of a solution of hydrochloric acid. The amounts of either edestin or arrowroot starch which were grossly visible in duodenal contents were minute; as were, also, the quantities of nonprotein nitrogen or of sugars, as determined by analysis. For these reasons, the buffer values were slightly, if at all, influenced by the content of food substances.

The absence of buffer action of the food substances used and the uniformity found in the buffer values of the duodenal contents indicate that the physical chemical factors governing the buffer conditions were approximately the same in all specimens of duodenal contents; i. e., the findings indicate that the various types of food substances had about the same stimulating effect on the external functions of the liver and pancreas as regards the production of buffer substances.

HYDROGEN-ION CONCENTRATION

In a former publication [4] it was shown that whenever food reaches the duodenum, there eventually occurs coincident augmentation in the flow of bile and pancreatic juice; i. e., food in some way produces a coincident stimulation of the external functions of the liver and pancreas. Since that publication appeared, the coincidence of this dual stimulation has been confirmed by the application of newly devised methods,[5] which furnish an index to the concentration of the bile present in duodenal contents. From these studies, it is concluded that in normal man the production of a materially augmented flow of bile is accompanied by stimulation of the external secretory function of the pancreas.

5. Unpublished observations.

The increase in flow of bile is readily detected on gross inspection, and occurs when the initially light colored duodenal contents abruptly change to a very dark shade of yellow. Thus, this color change inferentially furnishes an accurate index to the time when the onset of stimulation of the flow of pancreatic juice occurs in normal persons.

In the same publication [4] it was demonstrated that after pancreatic stimulation had occurred, it continued as long as food was passing through the duodenum. In former studies [6] it was shown that meals of a volume of 50 c.c. produce the same degrees of pancreatic, and apparently hepatic, stimulation as do meals of a volume of 300 c.c.

The foregoing discussion permits the conclusion that the duodenal contents analyzed in Table 3 were collected while the external functions of the liver and pancreas were as active as is usual during normal intestinal digestion. It will be recalled that these duodenal contents were collected over two consecutive thirty-minute periods after the abrupt change to dark colored bile occurred, following the ingestion of food. Table 3 shows that during the periods of collection the duodenal contents derived from edestin and the mixture of foodstuffs were acid; while those from olive oil and arrowroot starch were alkaline. Evidence has been presented [4] showing that olive oil is a more powerful stimulant to the activity of the external secretory function of the pancreas than is edestin or arrowroot starch. These findings show that the liver and pancreatic external functions were apparently stimulated to normal activity regardless of the reaction of the duodenal contents obtained from the proximal portion of the second part of the duodenum (about 5 to 10 cm. from the distal end of the pyloric sphincter).

Tables 1 and 2 concern duodenal contents collected (*a*) while the patient was fasting; (*b*) after the ingestion of tap water, and (*c*) from immediately after the ingestion of food up to the appearance of very dark colored bile. It has been shown [4] that during these periods of collection the activity of the external functions of the liver and pancreas is much less than after the onset of normal digestion. Nevertheless, the p_H of these duodenal contents lies within the same range as those found in duodenal contents collected over the period during which intestinal digestion was in active progress (Table 3), except for the more acid contents derived from Subject B of Table 3 after the ingestion of edestin. Thus, in these experiments, no demonstrable relation existed between the p_H of duodenal contents and the concentrations of bile and pancreatic juice in them.

The contents of the duodenum were acid for ten and twenty-one minutes before hepatic and pancreatic stimulation occurred in Subjects B and C of Table 2 after the ingestion of olive oil; while such stimula-

6. McClure et al.: Footnotes 2 and 4.

tion failed to occur in Subject C of Table 1, although the duodenal contents were acid. These findings, together with the absence of relationship between the p_H of duodenal contents and the concentrations of bile and pancreatic juice in them, offer additional support to the conclusion drawn from previous work;[4] namely, that under normal conditions acidity is probably not essential for the stimulation of the external functions of the liver and pancreas. However, it is always to be borne in mind that duodenal contents collected in the manner described represent a summation of progressive series of secretory activities. In other words, the properties of any sample are the algebraic sums of the several properties possessed by the many fractions which go to compose the sample. Thus, in a collection period of thirty minutes, it would be quite possible for the secretion of the first few minutes to be acid or alkaline in character, while in the latter portion of the collection time a preponderating amount of the opposite type of material could collect, neutralize the first portion and give a final reaction on its side of the neutral point. This fact connotes the necessity of exercising a large measure of caution in drawing final conclusions.

The work of Myers and McClendon[7] is of interest in relation to the foregoing discussion. These authors determined the p_H of duodenal contents after the ingestion of meals of the character usually eaten by normal persons. They found that the reaction of the duodenum between three and four hours after meals usually fluctuated around the neutral point. It is inferred from their publication that in many patients the alkaline contents were removed from the region of the duodenum lying immediately distal to the pyloric sphincter. Unfortunately, the details of the collection of duodenal specimens of importance in relation to the interpretation of the work presented here are not given. In general, the figures reported in their publication are comparable to those presented here.

CONCLUSIONS

1. The p_H of duodenal contents varied after the ingestion of various food substances. Duodenal contents were acid after the ingestion of protein and mixture of food substances, and alkaline after ingestion of fat and carbohydrate food substances.

2. No relation was found between the p_H of duodenal contents and the stimulation of the flow of bile and pancreatic juice.

3. The findings indicate that the various types of pure food substances had about the same stimulating effect on the external functions of the liver and pancreas as regards the production of buffer substances.

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7. Myers, F. J., and McClendon, J. F.: J. Biol. Chem. **41**:187 (Feb.) 1920.

Book Reviews

DIATHERMY AND ITS APPLICATION TO PNEUMONIA. By HARRY EATON STEWART, M.D., Attending Specialist in Physiotherapy, U. S. Marine Hospital, New York: Paul H. Hoeber, Inc., Price $3.

The introductory chapter of this book is devoted to a general discussion, including brief reference to the use of diathermy in the U. S. Marine service during the war, and to some general remarks, especially in regard to pneumonia.

The second chapter discusses diathermy technic, including the method of application to various portions of the body, and the diseased condition to which it is applicable. The reviewer is rather skeptical of its value in some of the conditions recommended by the author, as "simple myocardial conditions," to "accelerate absorption of clot after hemiplegia." "In those conditions where general cerebral degeneration sets in, due to arteriosclerosis, this current is a rival of galvanism in its effect on improving the nutrition of brain cells."

The third chapter discusses surgical diathermy, chiefly in malignant tumor and tonsils.

Chapters four, five and six are devoted to the treatment of pneumonia. The author reports marked lessening of the pleuritic pain and consequent slowing of respiration and lessening of cyanosis. Thirty-six patients with lobar pneumonia treated with diathermy gave a mortality of 19.4 per cent. In twenty-one controls, the mortality was 38.4 per cent. Practically all the treated cases terminated by lysis. As the average age of the patients was 35 years, a mortality of 19.4 per cent. is not especially striking, when we consider that the mortality in the first 5,000 cases of lobar pneumonia in the army during the war was less than 10 per cent. It is true the average age of these patients was considerably under 35 years.

The book rather suggests lack of a profound knowledge of pathology and internal medicine on the part of the author and contains a large number of loose statements. The possibilities of diathermy should not be ignored, and this book will be useful for those who wish to make a study of this subject.

NOSOGRAPHY IN MODERN INTERNAL MEDICINE. By KNUD FABER, M.D., Professor of Internal Medicine, University of Copenhagen; with an Introductory note by Rufus Cole, M. D., Director of Hospital, Rockefeller Institute. Twenty-one full page portraits. Price, $3.75. New York: Paul B. Hoeber, 1923.

Under an unfamiliar name, we have here a valuable contribution to medical history. Too often writers on medical history have felt it necessary to cover the whole subject from the beginning of the world, with endless notes and innumerable biographies. This tendency probably has had much to do with the neglect of the study of medical history. Knud Faber has traced the growth of nosography, that is the description of disease, in a masterly and attractive manner. As he correctly says, the importance of the nosographic method in investigation has been, and still is, very differently rated by different authorities. For this reason, he has made a study, the salient points of which follow.

On page 5, he takes up the work of the man "who first consciously and clearly gave clinical observation its place of honor as a scientific method"—Thomas Syndenham; and, in the following twelve pages, he gives a clear and adequate account of Sydenham's work, so far as necessary for this study, and at the same time indicating his limitations.

In ten pages more, the ground is covered to the consideration of the Paris school at the beginning of the nineteenth century, the work of Morgagni and

Auenbrugger being appropriately mentioned in connection with the period in which their work was really appreciated. Boerhaave is properly described as a brilliant teacher rather than an independent clinical investigator, qualities that characterize also his numerous pupils. As the author points out, in this period some advances were made in nosology. Varicella, influenza, ergotism, lead poisoning, scurvy, sciatica, trigeminus neuralgia, paraplegia in spinal caries and angina pectoris began to claim attention. The author's power of condensation is well shown in his account of Sauvages and Linné.

From this time, the author does not travel so rapidly. An estimate is made of Pinel, Bichat and Corvisart and the epoch-making Laennec, and their most important pupils are briefly placed. In a few words, Faber epitomizes the results of this epoch: "The violence with which clinical medicine was completely revolutionized . . . will always remain one of the wonders of medical history."

The Irish clinicians, and also Addison and Bright, are properly appreciated. The reference to W. W. Gerhard, the briliant American pupil of Louis, reminds one that, although Gerhard and his descendants anglicized the name, leaving the "h" silent, many now pronounce it in the teutonic fashion. Skoda, Rokitansky and Schoenlein appropriately close this chapter.

The next is devoted to "German physiological medicine," although, as the author points out, Magendie had already initiated the physiologic movement. Faber shows the weak points in that movement, in general so fruitful, such as the Vircho-Niemeyer tuberculosis teaching. As he says, German physiologic medicine was in the main preparatory, leading up to the new clinical era, through methods developed chiefly by physiologists and chemists. In speaking of Claude Bernard, he shows how easy it is for physiologists to miss the clinical point of view. An account of the great place filled by Trousseau leads to the name of Pasteur, and the bacteriologic clinic gives the name to a chapter in which the most outstanding discoveries and inventions in specific pathology are described. A large chapter is properly devoted to functional diagnosis. Many will think too much space is given to the views of Ottomar Rosenbach, interesting as they are. In this chapter, the wide range of the author's study is shown by his familiarity with the work of American investigators. He points out how the modern advance has finally led to the point that the patient himself can be treated, rather than the disease. Gastric ulcer is mentioned as an illustration of the errors into which diagnosis may fall. As the study of "hyperacidity" advanced, gastric ulcer became more and more rarely diagnosed, especially in German clinics, and ulcer only came back as a clinical diagnosis after surgery had taken over the old anatomicoclinical diagnosis. The French internist, Soupault, is given credit for the innovation. In this chapter, Faber discusses with great insight the proper point of view of the clinician.

The final chapter is devoted to constitutional pathology, a movement that "belongs almost entirely to the twentieth century, and is directly associated with the influence which modern research on heredity has had on pathology." Nowhere is the boundless extent of the basis of nosography better shown than in its turning to the experiments of Mendel and his successors. In this chapter, too, is a discussion of causes, conditions and disposition. In his final remarks, the author sums up the essence of nosographic study.

The little work will be interesting to clinicians familiar with medical history on account of the skill with which the large subject has been brought within reasonable limits. It should be carefully read by all medical students in their early years, especially in the long period in which they hear little of clinical medicine, and that very often in an unsympathetic tone.

The publisher has done his work fairly well. In these pictorial days, a few more portraits could have been added with advantage. Errors in the text are few. Welcher (p. 80) should be Welcker, and typhus (p. 118) typhoid.